An Investigation of MiRNA Significances in Urinary Bladder Cancer

By
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A thesis submitted to the School of Pharmacy in partial fulfilment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
BRAC University
September 2024

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

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Approval

The thesis/project titled "An Investigation of MiRNA Significances in Urinary Bladder Cancer" submitted by Sheikh Ayesha (20146038), of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This project does not involve any kind of animal and human trial.

Abstract:

Urinary bladder carcinoma is a malignant transformation of glandular cells that develops from the epithelial lining of the urinary bladder which is linked to the dysregulation of miRNA. This often associated with risk factors such as smoking, occupational exposure to certain chemicals, and chronic inflammation. We found 309 articles on PubMed and google scholar about miRNAs and their involvement in diagnosing and advancing bladder cancer. After carefully reviewing the literature, we selected and analyzed 9 papers involving a total of 544 individuals. The studies we reviewed indicate that miRNAs are crucial in diagnosing, predicting outcomes, and treating bladder cancer. Although different studies identify various miRNAs, they unanimously emphasize the impact of miRNA irregularities in bladder cancer development. Specifically, elevated miRNA levels are linked to increased proliferation, migration, and invasion of bladder cancer cells. Our aim is to investigate the roles that miRNA expression plays in various body functions and how it assists in the identification and advancement of bladder cancer.

Keywords: Urinary bladder cancer, miRNA, Biomarker, diagnosis.

Acknowledgement

First and foremost, I convey my profound appreciation to the Most Merciful Allah for bestowing me strength all through my life and assisting me where I am today. I would offer my infinite thankfulness and earnest gratitude to my respected supervisor Associate Professor Mohd. Raeed Jamiruddin, for whom I am able to complete the work. His essential direction and persistent encouragement have played a significant part across my pharmacy journey and during my final year. I am pleased to receive the chance to finish my thesis under his steadfast mentorship. I am also indebted to my friends, who were there with me at every stride of my undergraduate life. Finally, I grant my sincere gratitude to my parents who motivated me to come this far in life. Without their help, I would not have the bravery to major in pharmacy. I shall eternally be indebted to them and my Lord for their directions.

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List of Acronyms

RISCs: RNA-induced silencing complexes

NMIBC: Non-muscle-invasive bladder cancer

MIBC: Muscle-invasive bladder cancer

AGO1-4: Argonaute proteins

Cdks: Cyclin -dependent protein kinases

TGFβ: Transforming growth factor-beta

CDKN1A: Cyclin dependent kinase inhibitor 1A

FOXQ1: Forkhead box Q1

IRF3: Interferon regulatory factor 3

TTP: Tristetraprolin

ZFP36: Zinc finger protein 36 homolog

DMTF1: Cyclin-D-binding Myb-like transcription factor 1

DDX6: DEAD-Box Helicase 6

HIF-1α e: Hypoxia-inducible factor 1-alpha

PPARG: Peroxisome proliferator-activated receptor gamma

PPARA: Peroxisome proliferator-activated receptors

PPAR-γ: Peroxisome proliferator-activated receptor gamma

SIRT1: sirtuin (silent mating type information regulation 2 homolog)

PI3K/Akt: phosphoinositide-3-kinase–protein kinase B/Akt

ROS: Reactive oxygen species

VEGF: Vascular endothelial growth factor

CSDC2: cold-shock domain-containing protein C2

Introduction

Bladder cancer is the fourth predominant prevalent cancer in men and the ninth in women in the western world. Urinary bladder cancer impacts more than 2 million people globally. It usually affects the elderly, with 80% of diseases happening in those between the ages of 50 and 79. When correlating developed to less developed regions, the occurrence of bladder cancer is more in developed countries. Study has revealed that greater than 5% of recently identified tumors in European countries are associated to bladder cancer. Urinary bladder adenocarcinoma (UBA) happens when glandular cells in the bladder turn cancerous. These malignancies are notable by irregular expansion of glandular cells, developing structures corresponding tubes or glands. UBA is rare and aggressive, likely affected by genetics, exposure to specific pollutants, and chronic inflammation. Besides, UBC is categorized into two clinical characteristics: non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). NMIBC is more prevalent than MIBC at the time of diagnosis, responsible for 75–80% of cases. Although it originates from the bladder's urothelium, primary adenocarcinoma of the bladder has a phenotypic that is exclusively glandular. Males predominate and the patients are often in their sixth or seventh ages of life. The most typical symptom is hematuria, however mucusuria and feelings of bladder irritation can also occur in certain cases. Many studies showed that about one-third of the patients have lymph node metastases. While the exact cause of bladder adenocarcinoma is still unknown, a number of risk factors have been identified. Most remarkably, adenocarcinomas account for over 90% of bladder tumors in patients with bladder exstrophy. In regions where schistosomiasis is endemic, adenocarcinomas account for up to 10%

of all bladder cancer cases. Cystocele, endometriosis, blockage, and persistent discomfort are additional potential risk factors. Although intestinal metaplasia and cystitis glandularis are frequently observed next to bladder adenocarcinoma, new research has revealed that these conditions do not raise the risk of adenocarcinoma. Furthermore, bladder adenocarcinoma histologically displays different development structure: (a) enteric (intestinal or colonic); (b) mucinous (colloid); (c) signet ring cell; (d) not else specified (NOS); and (e) mixed patterns. The intestinal-type glands in the enteric pattern resemble colorectal adenocarcinomas because they have nuclear atypia and pseudostratified columnar cells. It can produce mucin either extracellularly or intracellularly, and necrosis is common. Tumor cells suspends in a pool of extracellular mucin produced by the mucinous pattern. Diffusely infiltrative, poorly differentiated cells with significant intracellular mucin and indented eccentric nuclei make up the signet ring cell pattern. Compared to other variations, these tumors typically have a worse prognosis and occur at an advanced stage. There is non-specific glandular development in the NOS type. Mixed type tumors have multiple patterns present in them. Apart from the aforementioned variations, there aren't many documented examples of the hepatoid variety of adenocarcinoma in the literature. Alpha-fetoprotein, HepPar-1, and alpha-1 antitrypsin are stated by these tumors, which look like hepatocellular carcinoma. The cytoplasm of the tumor cells is rich in eosinophilic material and contains hyaline globules organized in trabeculae and solid sheets. The creation of bile is visible. While a number of grading schemes have been put out for primary bladder adenocarcinoma, their acceptance has not been consistent [43]. That is why, pinpointing its exact occurrence is difficult due to its rarity. Diagnosing and treating UBA can be challenging. Despite efforts to inhibit and cure bladder cancer, 60% of patients with this ailment

live five years after diagnosis. Nonetheless, patients with metastatic bladder cancer usually have a poor prognosis. Thus, patients with bladder cancer still have a low possibility of survival if they obtain early detection and therapy (Wang et al., 2018c) (Zaidi et al., 2023b).

A group of non-coding RNA molecules with a standard length of about 22 nucleotides is known as microRNA (miRNA). MicroRNAs are small RNA molecules that don't code for proteins but play a vital role in controlling gene expression after transcription. They achieve this by binding to specific regions in the messenger RNA (mRNA) molecules, causing either translational suppression or mRNA destruction. Since a single microRNA can regulate numerous genes, they exert significant control over gene expression at the post-transcriptional level. RNA polymerase II/III transcripts that have been post- or co-transcribed are the starting point for miRNA production. While certain miRNAs are intergenic and transcribed without reference to a host gene, the majority of miRNAs are intragenic and mostly originate from introns and certain exons. Families of miRNAs can develop by cluster transcription. Canonical or non-canonical pathways can be followed by biogenesis, with the canonical pathway predominating. In this mechanism, the microprocessor complex (DGCR8 and Drosha) converts pri-miRNAs into pre-miRNAs, producing a 2 nt 3′ overhang. A mature miRNA duplex is produced when pre-miRNAs are transported to the cytoplasm and digested by Dicer. The 3p strand of the hairpin originates from the 3′ end, and the 5p strand from the 5′ end. It is possible to load both strands into Argonaute proteins (AGO1-4). While the passenger strand is deteriorated, the selection of the guide strand is centered on thermodynamic stability or a 5′ U at nucleotide position 1. Conversely, countless non-canonical miRNA biogenesis routes have been determined thus far. These routes mostly use compositions of Dicer, Drosha , AGO2 and exportin 5 which are proteins engaged in the canonical process.

Non-canonical miRNA biogenesis can be widely categorized into routes that are Dicer-independent and those that are Drosha/DGCR8-independent. The Drosha/DGCR8-independent process creates pre-miRNAs that simulates substrates for Dicer. Mirtrons, which are created over splicing from the mRNA's introns, are an example of a pre-miRNA. The 7-methylguanosine (m7G)-capped pre-miRNA serves as alternative illustration. Without compelling Drosha cleavage, exportin 1 carries these growing RNAs straight to the cytoplasm. The m7G cap's capacity to block 5p strand stocking into Argonaute is probably the reason of the mostly 3p strand inclination. Contrarily, Drosha functions endogenous concise hairpin RNA (shRNA) transcripts to creates dicer-independent miRNAs. These pre-miRNAs are too compact to be Dicer-substrates, thus AGO2 is essential for them to complete evolving in the cytoplasm. Consequently, this stimulates the full pre-miRNA to be stocked into AGO2 and AGO2-dependent 3p strand slicing. The 5p strand's 3′–5′ cutting completes their maturation (O'Brien et al., 2018b). Besides, past researches have exhibited that miRNAs are associated in approximately every facet of important cellular activities inside the human body. It has been shown that particular types of malignant cell development are linked with microRNAs, or miRNA. Distinctive non-invasive diagnosis is particularly required in cases of urothelial bladder cancer, and it is appealing to take into account because urine is an easily accessible supply of molecular markers, including miRNAs. While up-regulated miRNAs may boost the expansion of cancer, down-regulated miRNAs in tumors are considered to be tumor suppressor capabilities. In bladder cancer, dysregulated microRNAs have been linked to increased cell growth, progression, and resistance to apoptosis, making them favorable biomarkers for detecting cancer, including bladder cancer, due to their stability in bodily fluids (Wang et al., 2018c) (Zaidi et al., 2023b).

Cell regulation is like a complex system that helps cells respond correctly to signals from inside and outside the body. Signaling pathways act like messengers, passing messages from outside the cell to the inside, which then trigger changes in how genes are used and how cells use energy. Cyclin -dependent protein kinases (Cdks) play a direct role in controlling the cell-division cycle in eukaryotic cells. They are activated cyclically to initiate different phases of the cell cycle at specific times and in a precise order. Cdks are controlled by diverse proteins: cyclins initiate them and conduct them to their targets; kinases and phosphatases include or exclude phosphate groups from Cdks, respectively; and Cdk inhibitors block their action or healthier interaction with cyclins. While the initial cell divisions in zygotes and blastomeres are independent of external factors, most animal cell divisions rely on growth factors produced by neighboring cells. Besides, Gene regulation is all about controlling which genes are turned on or off and how much of each protein is made, helping cells adjust to different situations. On the other hand, metabolic regulation makes sure cells make enough energy and use nutrients effectively, adapting to what the cell needs. Lastly, cell division is carefully controlled to make sure cells make exact copies of themselves and grow properly. If any of these processes go wrong, it can lead to serious health problems like cancer or metabolic disorders, showing just how important they are for keeping cells healthy and balanced (Obaya & Sedivy, 2002b).

This review is conducted to showcase the significance of miRNAs in bladder cancer. The research illustrates how miRNA irregularities can promote the development and spread of cancer cells. Furthermore, it shows that miRNAs could potentially serve as biomarkers for detecting and monitoring bladder cancer.

Methodology

A systematic search was carried out to discover researches that characterize the urine expression of one or more microRNAs (miRNAs) as a noninvasive method for diagnosing and generative growth of bladder cancer (BC). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were pursued while performing this systematic review (figure1). Using the Boolean approach, we carried out this systematic review with diligence, resulting in an exhaustive search for scientific electronic databases like PubMed that included papers published until and including April 2024.The generated search results were then carefully aggregated and carefully filtered to remove duplicates. The articles were independently scrutinized to guarantee that the titles and abstracts met the eligibility requirements. Each article's entire content was then procured, and its suitability was evaluated. The articles were subjected to a rigorous set of selection criteria, which included the following requirements: (1) documentation of miRNA expression levels; (2) a description of the diagnostic utility of the suggested biomarkers; (3) English language accessibility; (4) conduct as either cohort studies or randomized controlled trials. However, non-English papers, reviews, metadata, case reports, letters to the editor, methodological studies were not incorporated in our assessment. After sorting through all of the collected data, we compiled the information that fulfilled the predetermined incorporated parameters into an appropriate Excel file. Data retrieval from the selected studies were done employing a standardized table. For each study, the collected data are documented in Table 1follows: Study name, sample and size, number of patients and healthy individuals, DOI number, patient demographic, documentation of miRNA expression level, positive predictive value (PPV), sensitivity value, result of each selected study.

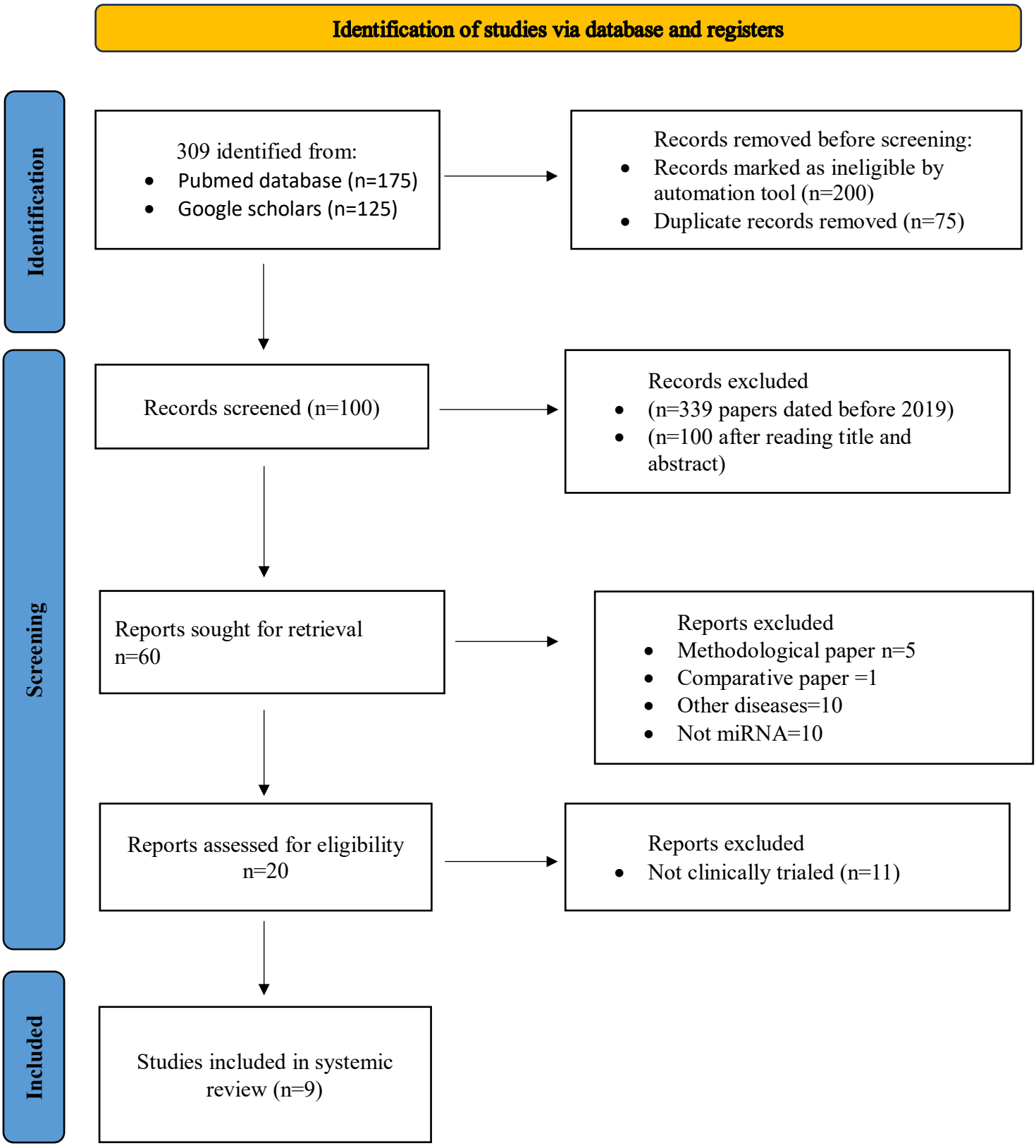

Figure 1. PRISMA 2020 flow diagram which includes searches of the databases

Table 1. Main features of each selected study

Study Name	DOI Number	Number Of bladder Cancer Patients	Participants demographic			Sample	Sample Size	Number of healthy individuals	Positive predictive value	sensitive value	miRNA Upregulation or downregulation in UBC	Result
			Age	Male (%)	Female (%)							
1)Evaluation of urinary miRNA-96 as a potential biomarker for bladder cancer diagnosis	10.1007/s12032-014-0413-x	96	28-85	78.7	21.3	Voided Urine	30-60 ml	60	73% to 87.2%(High)	High	upregulated	miRNA-96 serves as diagnostic biomarker for BC specially in patient with bilharziasis
2)Expression of microRNA-155 and human telomerase reverse transcriptase in patients with bladder cancer	10.1080/2314808X.2020.1816337	30	60	73.3	26.7	Voided urine	50-100 ml	15	80 %(High)	96.67%(high)	Downregulated	miRNA-155 is potential non-invasive biomaker for BC
3)Urinary microRNA-10a levels in diagnosis and prognosis of urinary bladder cancer	10.4103/jcrt.jcrt_1014_21	20	56.1	100		voided urine and tissue	625 µL	20		100%	Upregulated	Patients with urinary bladder cancer (UBC) exhibited higher miRNA expression compared to healthy controls, positive urine cytology, and

												disease recurrence, while no significant differences were observed
4)Evaluation of miR-130 family members as circulating biomarkers for the diagnosis of bladder cancer	10.1002/jcla.23517	74	63.8	73	27	serum	4ml	90		87.80%	Upregulated	The miR-130 family, including miR-130a-3p, miR-130b-3p, and miR-301a-3p serves as potential diagnostic biomarkers with their combined expression showing high diagnostic efficacy

5) A Panel of Three Serum MicroRNAs as a Potential Diagnostic Biomarker for Urothelial Carcinoma	10.1159/000523853	152	64	83.3	16.7	serum		135		93.80%	Upregulated (miR17-5p, miR224-5p) Downregulated (145-5p)	The study identified a panel of three serum miRNAs, miR17-5p, miR145-5p, and miR-224-5p, which showed significant diagnostic potential where miR-224-5p being associated with higher pathological grade and advanced tumor stage while miR17-5p exhibited dysregulation based on tumor location.

6)Combined miRNA and SERS urine liquid biopsy for the point-of-care diagnosis and molecular stratification of bladder cancer	10.1186/s10020-022-00462-z	15				serum		16	0.87 for naïve Bayes,0.84 for logistic regression, and 0.81 for random forest		Upregulated	Study demonstrated that combining urine miRNA and SERS profiling can accurately distinguish bladder cancer patients from controls
7)miRNA-373 promotes urinary bladder cancer cell proliferation, migration and invasion through upregulating epidermal growth factor receptor	10.3892/etm.2018.7061	55	45	40	15	blood	10ml	45			Upregulated	miRNA-373 overexpression may promote urinary bladder cancer cell proliferation, migration, and invasion by upregulating EGFR
8)Urinary Exosomal miR-17-5p Accelerates Bladder Cancer Invasion by Repressing its Target Gene ARID4B and Regulating the Immune	10.1016/j.clgc.2024.01.012					urine and tissue	10 urine specimens. 25 paired tissue samples				Upregulated	Identification and implications of exosomal miR-17-5p in BCa, highlighting its clinical value as a target for BCa treatment.

Microenvironment												
9)Correlation of Increased Expression of MicroRNA-155 in Bladder Cancer and Prognosis	10.1309/LMWR9CEA2K2XVSOX	102	60	61	41	tissue	102 pair	102			Upregulated	Elevated miR-155 expression is correlated with a poor outcome for patients with bladder cancer, indicating its potential as a biomarker for bladder cancer prognosis

Result and discussion

MiRNA-96 plays a vital part in modulating gene expression in polymorphic species by impacting mRNA constancy and interpretation (*Account - GeneCards Suite*, n.d.-b). These miRNAs are transcribed by RNA polymerase II as part of primary transcripts (pri-miRNAs), which can be protein-coding or non-coding (Bagban et al., 2023c). After processing by enzymes like Drosha and Dicer, mature miRNAs are incorporated into RNA-induced silencing complexes (RISCs). The single factor that can modulate microRNAs is the RNA-induced silencing complex (RISC). By assembling RISC and targeting for the messenger RNA (mRNA) specified by the microRNA, the microRNA begins the RISC complex. It binds imperfectly to target mRNAs, typically leading to either translation suppression or mRNA destabilization (*MIR96 microRNA 96 [Homo Sapiens (Human)] - Gene - NCBI*, n.d.-b). Besides, urinary bladder cancer, miRNA-96 is associated with the development of several cancers, such as liver, cervical, prostate, and breast cancers. In bladder cancer, notable tumor suppressor genes FOXO1, FOXO3, and their modifications are directly targeted by miR-96-5p. It was found that miR-96, which targets the expression of the FOXQ1 gene, sped up bladder cancer in conditions where TGF-β was the major contributor. The FOXQ1 gene is associated to cell death. The amplification of miR-96 was found to be facilitated by TGF-β, which sequentially decrease the expression of FOXQ1, provoking BC cells to increase and aiming and provoking EMT (Epithelium Mesenchyme Transition) in these cells. One of major targets of BC is the tumor suppressor gene CDKN1A (p21), which stimulates halt of cell growth. Malignant BC yields from the overexpression of miR-96, which attaches to CDKN1A and lessens its expression (Bagban et al., 2023c).

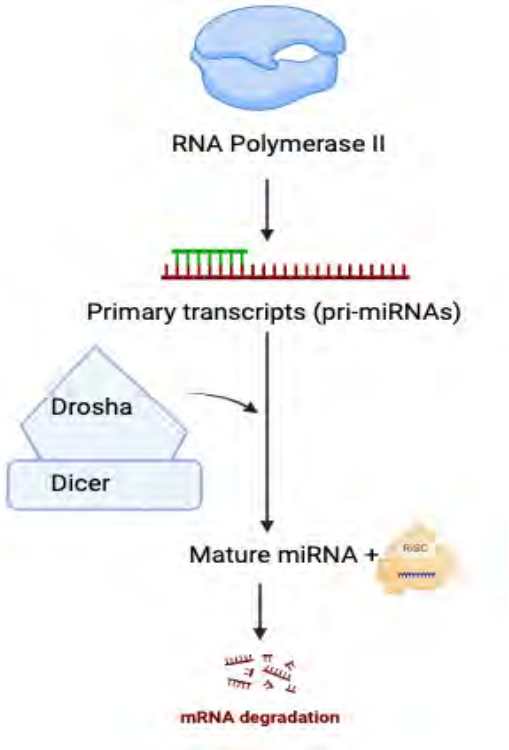

Figure 2. Pathway of miR-96 regulation in gene expression

Several signaling mechanisms regulate the expression of miR-155. TGF-β is one of the regulatory cytokines that can in lieu of excite or subdue the formation of miR-155. Both miR-155-5p and miR-155-3p are downregulated in astrocytes by the anti-inflammatory IRF3 protein. Resolving D1 hinders the expression of miR-155, which shrinks inflammation in experimental corneal immunopathology.IL-10 steadily suppresses the transcription factor Ets2 to declines the expression of miR-155 (Mahesh & Biswas, 2019b).Besides,MiR-155 expression is regulated during biogenesis with a specific emphasis on the RNA-binding protein tristetraprolin (TTP/ZFP36) during bodily function where TTP functions as a negative regulator post-transcriptionally by identifying adenine–uridine-rich elements (AREs) in the 3′-UTR of target

mRNAs, resulting in their degradation (Mahesh & Biswas, 2019b).IRF3 exhibits the capacity to mitigate neuroinflammation by modulating miR-155 expression, while the regulatory role of miR-155 in inflammation associated with IL-17/IL-9 during wound healing implies its potential utility in enhancing inflammatory responses in wound tissues (Mahesh & Biswas, 2019b). Besides, MiR-155 shows a significant association with various cancers such as lung, pancreatic, colon, and breast cancers when considering gene expression related to these diseases (Mahesh & Biswas, 2019b). In bladder cancer, miR-155 works as an oncogene, triggering cell division and expansion both in vivo and in vitro. It was proven that miR-155 directly inhibits DMTF1.The function of tumor suppressor DMTF1 is to activate Arf to cause cell cycle to stop and decrease cell growth, although partly without the help of p53.However, DMTF1-Arf-p53 signaling pathway is interfered by miRNA-155 in bladder cancer (Peng et al., 2015a).

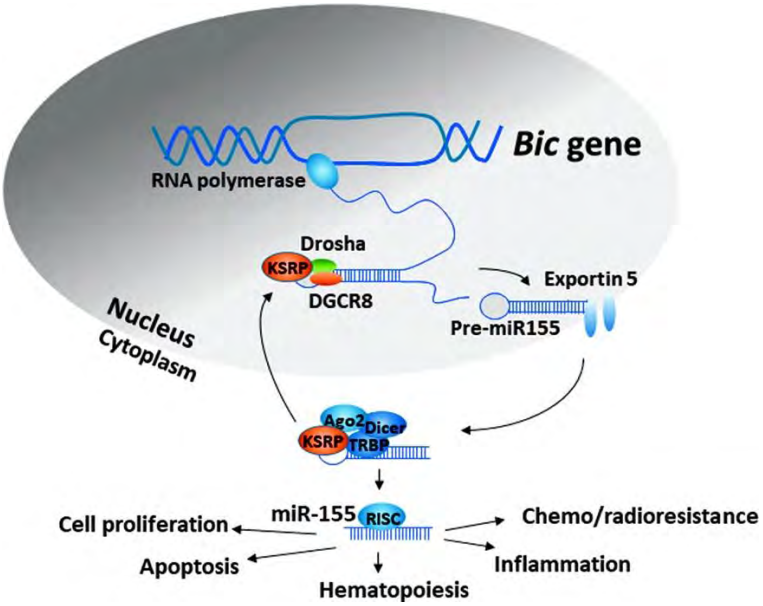

Figure 3. Schematic representation of miR-155 gene expression in immune response (Mahesh & Biswas, 2019b).

MiR-10a controls glioma migration by modulating the EphA8 pathway. 3′-UTR of EphA8 is directly adhere by miR-10a, which can adversely influence the expression of EphA8 at the mRNA and protein levels. EphA8 knockdown can reflect miR-10a over-expression (Yan, Wang, Yan, Zhang, Li, Tang, Li, et al., 2015). MiR-10a also regulates IκB/NF-κB-mediated inflammation pathway in arterial endothelial cells. In nonactivated endothelium cells, NF-κB stay in the cytoplasm after attaching to IκBs. Nuclear translocation of p65, or NF-κB, can solely be activated when IκBs are phosphorylated, polyubiquitinated, and then proteolyzed. In miR-10a knockdown cells, nonphosphorylated IκBα was substantially decreased but nuclear p65 elevated at the cost of cytoplasmic p65. Therefore, endothelial transcriptome alterations procure by endogenous miR-10a suppression improved IκBα deterioration, NF-κB activation and the up-regulation of inflammatory biomarkers (Fang et al., 2010b). Furthermore, it controls the differentiation of smooth muscle cells (SMCs) from embryonic stem cells (ESCs) by suppressing HDAC4 and the NF-κB pathway. HDAC4 and its action during SMC differentiation may be repressed by miR-10a. miR-10a expression and HDAC4 protein level during ESC/SMC development have an opposite linkage without a noticeable shift in HDAC4 mRNA level. Furthermore, when advanced miR-10a expression was inhibited by miR-10a inhibitor in this ESC/SMC differentiation system, the down-regulation of HDAC4 protein level was regenerated devoid of manipulating HDAC4 mRNA levels. The practical proposition suggests that miR-10a bonding to the HDAC4 3′-UTR would result in HDAC4 translational suppression (Huang et al., 2010b). However, MiRNA-10a drives the progression of lung cancer, gastric carcinogenesis, cervical cancer, and oral squamous cell carcinoma (Yu et al., 2015) (F. Liu et al., 2021b) (Gu, Feng, et al., 2023) (Y. Chen et al., 2019b). Moreover, in bladder cancer, miRNA-10a interacts with lncRNA ITGB1 and ITGB1 potentially

regulating miRNA-10a expression. Decreased ITGB1 levels enhance miRNA-10a expression, impacting cell proliferation and influencing the progression of bladder cancer (Dai et al., 2019b).

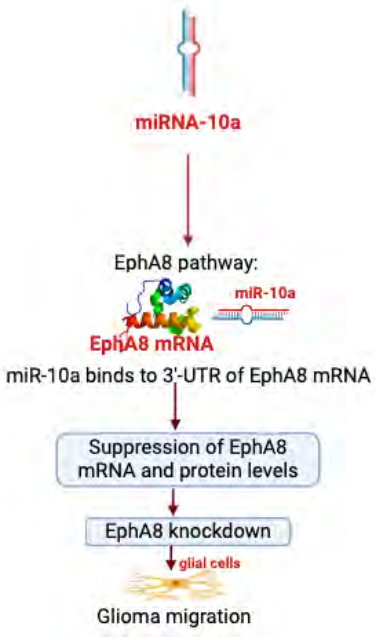

Figure 4. Schematic representation of miR-10 in glioma migration

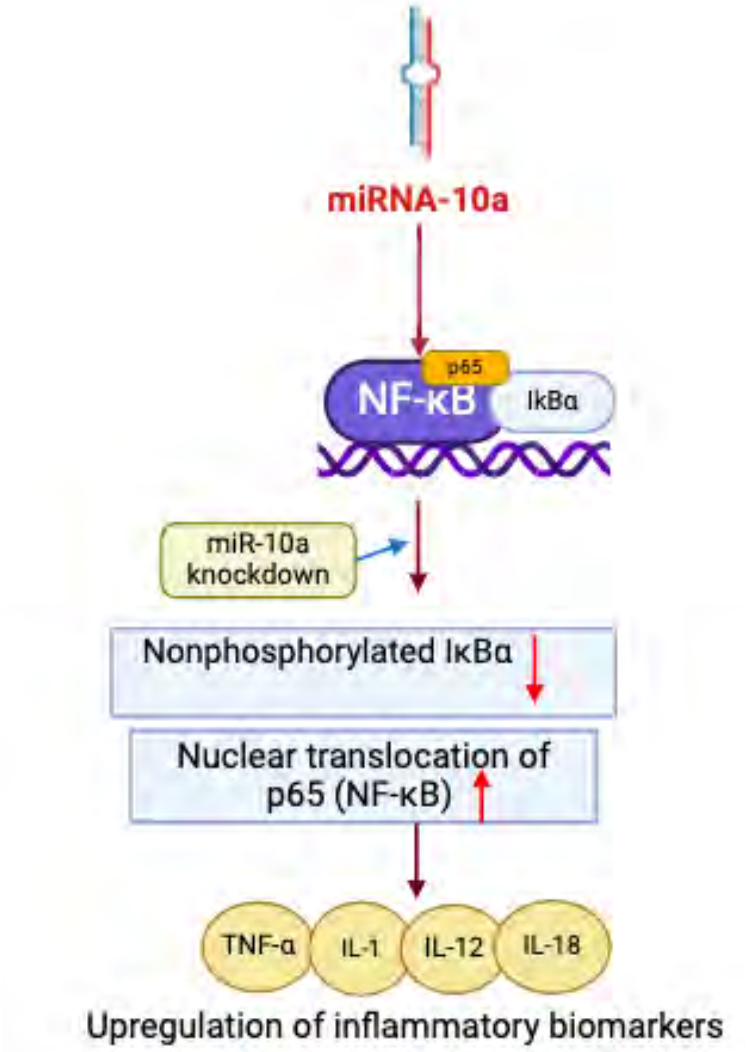

Figure 5. Schematic representation of miR-10 in upregulation of inflammatory biomarkers

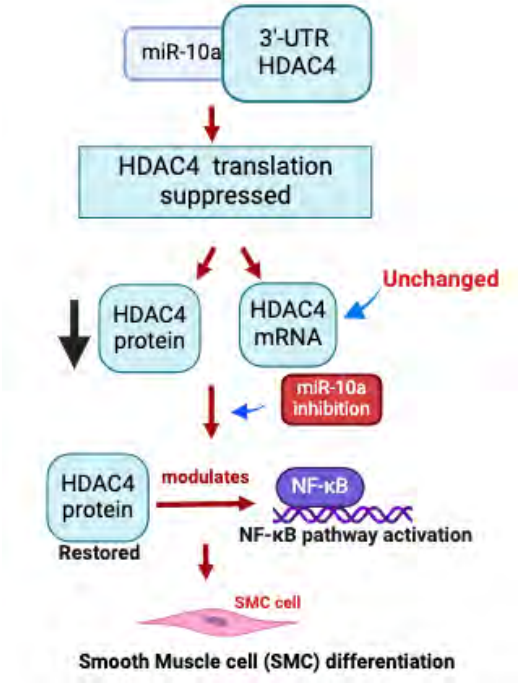

Figure 6. Schematic representation of miR-10 in smooth muscle cell (SMC) differentiation.

MiR-130a acts upon to hypoxic stress by targeting the mRNA of DDX6, a component of P-bodies. The DDX6 gene knockdown considerably improved HIF-1α. Actually, miR-130a and -130b minimized the expression of a luciferase reporter gene comprising the DDX6 3′UTR, but a DDX6 3′UTR alteration at the miR-130a- and -130b-binding region did not modify luciferase action. Besides, pre-miR-130a and -130b down-regulated the levels of endogenous DDX6 protein. Contrarily, DDX6 overexpression reduced HIF-1α expression, whereas DDX6 knockdown did not. These conclusions indicated that the miR-130 family moderated HIF-1α expression via DDX6 (Saito et al., 2011b). Moreover, miR-130 modulates adipose tissue function by targeting key transcription factors involved in adipogenesis, such as PPARG and PPARA.miR-130 had a notably

consequences on the differentiation of adipocytes; miR-130 overexpression hindered adipogenesis, while miR-130 reduction enhanced adipogenesis. The protein peroxisome proliferator-activated receptor γ (PPARγ), a vital regulator of adipogenesis, was one of the key effectors of miR-130 activities. It is prominent that miR-130 efficiently suppressed the production of PPARγ by centering on both the 3′ untranslated region and the PPARγ mRNA coding regions. Furthermore, miR-130 responds to insulin sensitivity by targeting key transcription caveolin 1, a regulator of insulin signaling, and also influences inflammatory pathways through its regulation of SIRT1 expression (Calderari et al., 2017). However, MiRNA-130 contributes to the onset of lung cancer, colorectal cancer, and gastric cancer in human individuals (W. Hu, Zheng, Liu, et al., 2021) (L. Liu et al., 2013) (Tian et al., 2016b). On the contrary, the upregulation of the miR-130 family in bladder cancer specimens amplifies bladder cancer cell migration and invasion by modulating the PI3K/Akt signaling pathway via PTEN regulation or sub-cellular localization, resulting in the phosphorylation of focal adhesion kinase (FAK) and Akt (Egawa et al., 2016b).

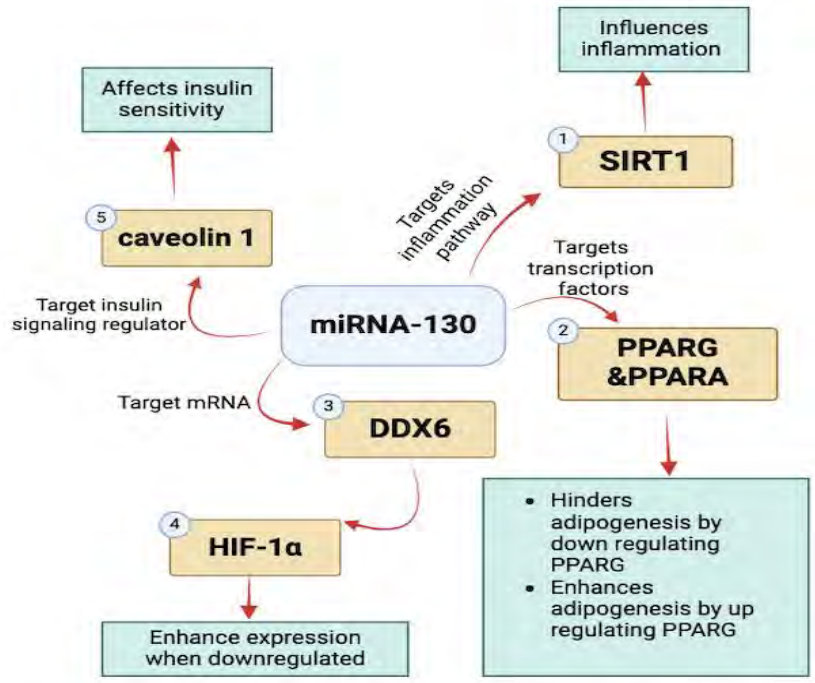

FIGURE 7. Schematic representation of miR-130 affecting hypoxia, stress adipogenesis, insulin sensitivity and inflammation

MiR-17-5p modulates the ERK pathway, affecting apoptosis and vascular injury, thus impacting cardiac function post-acute myocardial infarction (AMI) where the ERK pathway was activated in apoptosis-induced HUVECs by miR-17-5p silencing, that is exhibited by increased ERK mRNA and protein levels as well as phosphorylated ERK (P-ERK) (Yang, Fan, Hu, Xu, et al., 2018).On the other hand, miR-145-5p regulates the AKT/GSK signaling pathway via CXCL16 targeting, resulting in suppressed proliferation and inflammatory responses in renal mesangial cells. In RMCs, miR-145-5p lowered inflammatory reactions, extended the S phase, protracted the G0-G1 phase, and obstructed cell proliferation. Additionally, by binding to the 3′-UTR of CXCL16, miR-145-5p blocked the expression of CXCL16 protein. It also regulated the AKT/GSK signaling pathway and minimized the expression of mRNAs linked to inflammation, including IL-1α, IL-2,

IL-6, and TNF-α mRNAs. Furthermore, in RMCs, blocking CXCL16 reduced inflammatory responses and downregulated the AKT/GSK pathway (J. Wu et al., 2017b).MiR224-5p contributes to the development of lung adenocarcinoma, while MiR-17-5p promotes colorectal cancer (Xue, You, Liu, et al., 2023) (Z. Liu, Ji, Jin, Jiang, & Liu, 2022).MiR-17-5p influences the maturation of bladder cancer cells by modulating ARID4B, and lowered expression of the reporter gene with the ARID4B-WT 3'UTR in dual-luciferase reporter assays, while miR-145-5p regulates the UHRF1 pathway for bladder cancer progression (Yuan et al., 2024b) (Choudhry et al., 2017b).

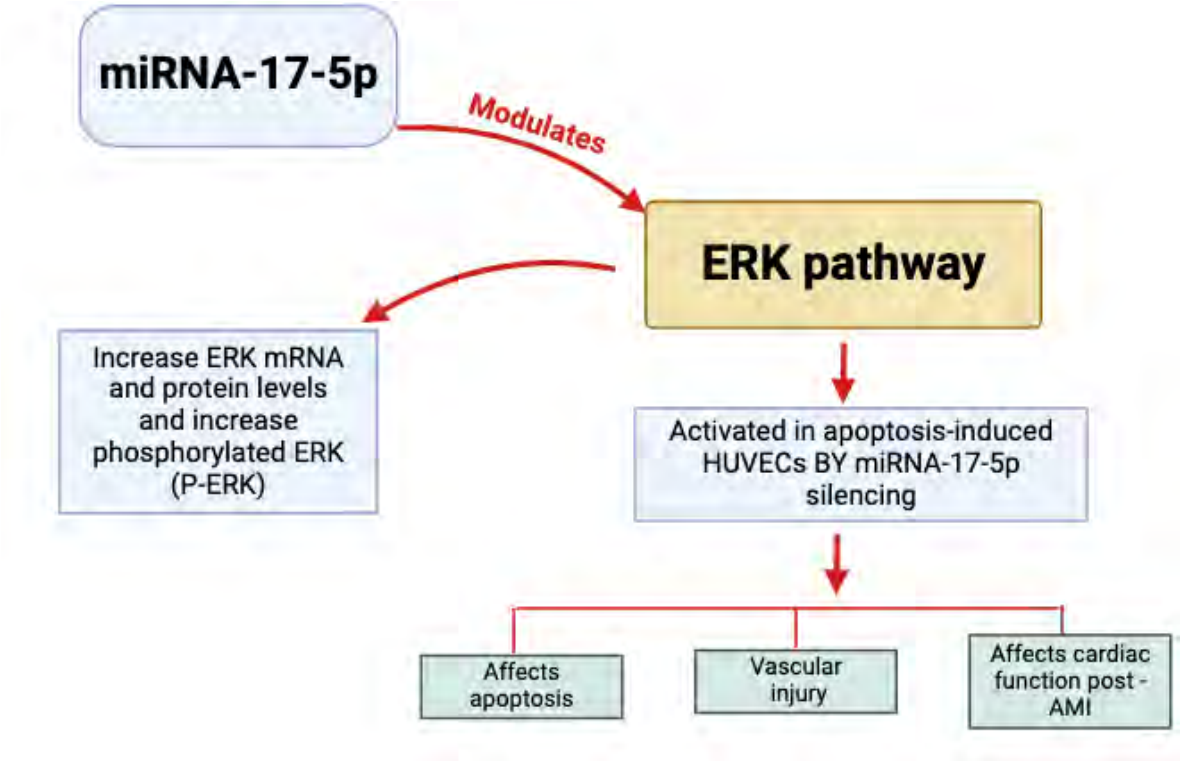

FIGURE 8. Schematic representation of miR-17-5p in regulating cellular pathways

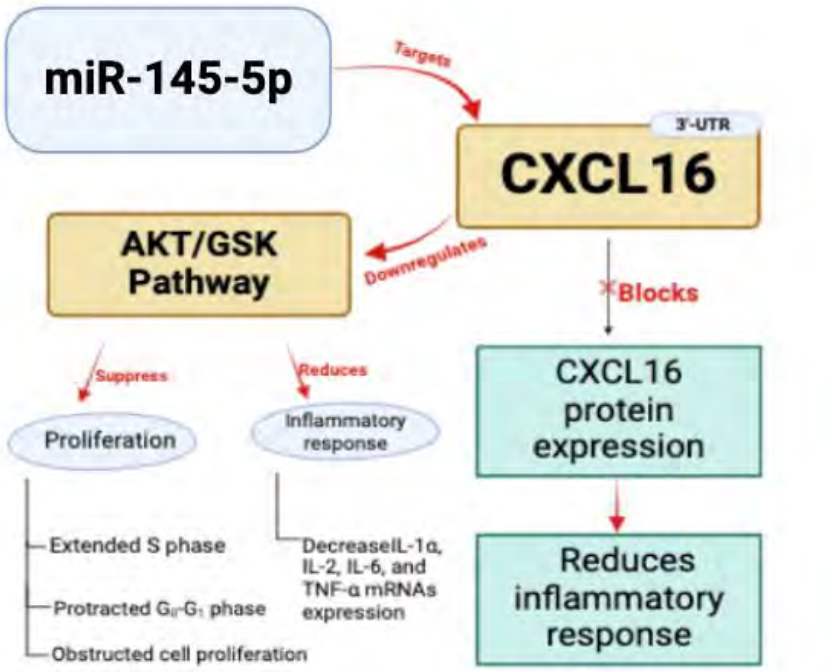

Figure 9. Schematic representation of regulatory pathway of miR-145-5p effecting CXCL16, AKT/GSK pathway proliferation and inflammatory response.

MiR-210 modulates mitochondrial metabolism by targeting iron-sulfur cluster assembly proteins, leading to diminished oxidative phosphorylation where MiR-210 principally targets iron-sulfur cluster assembly proteins 1/2 and shrinks the activity of complex I and aconitase, two proteins that handle the mitochondria's metabolic process, yielding in decreased oxidative phosphorylation. Multiple study has explored how miR-210 regulates mitochondrial activity and have established a vast selection of miR-210 targets. The primary positions for the synthesis of reactive oxygen species (ROS) are mitochondria. Moreover, the miR-210 is a resourceful controller for a broad range of cellular operations. Research has demonstrated that miR-210 has quite a few regulatory functions and was initially identified as a miRNA regulated by hypoxia

, while also impacting DNA repair processes by repressing genes such as RAD52, thus supporting DNA double-strand break repair and sustaining genetic stability. So, miR-210 inhibits RAD52's translation but not its transcription, which is vital for DNA double-strand break repair. This protein is also significant for homologous recombination and, by inhibiting the cellular DNA repair approach in hypoxic environments, may provide a novel regulatory mechanism for DNA repair. Aside from suppressing DNA-repairing genes, such as RAD52, miR-210 enables DNA double strand break repair following radiation exposure, thus uplifting genetic inconsistency and escalating the growth of cancerous cells. Moreover, miR-210 regulates angiogenesis by targeting factors like VEGF and ephrin-A3, impacting vascular growth [(Hui et al., 2019).Besides bladder cancer miR-210 is highly expressed in breast cancer and lung cancer (X. Wu, 2020b) (Puisségur, Mazure, Bertero, Pradelli, Grosso, Robbe-Sermesant, Maurin, Lebrigand, Cardinaud, Hofman, Fourre, et al., 2010).MiR-210 promotes angiogenesis in bladder cancer by inhibiting negative regulators of VEGF, like ephrin A3 and phospho-tyrosine phosphatase 1B, facilitating tumor growth and metastasis, while also influencing cell proliferation and migration through its regulation of genes including FGFRL1, RAD52, BDNF, PTPN1, NCAM1, and the lncRNA XIST (Sharma & Gupta, 2020b).

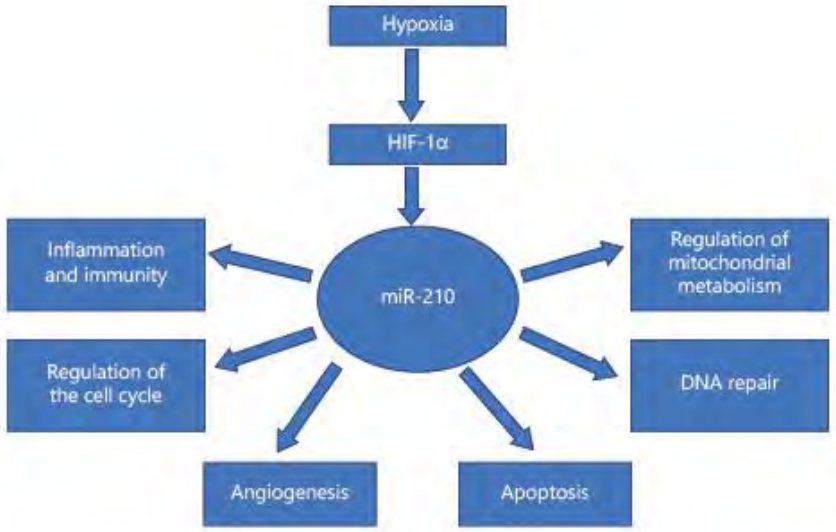

FIGURE 10. Schematic representation of the role of miR-210 in body (Hui et al., 2019).

MiR-373 may induce gene expression by targeting promoter sequences of specific genes like E-cadherin and cold-shock domain-containing protein C2 (CSDC2), potentially influencing pathways associated with cell adhesion and stress response, respectively. Through the process of in silico gene promoter inspecting for sequences identical to accepted miRNAs where a potential miR-373 target site was discovered within the E-cadherin promoter. When miR-373 and its precursor hairpin RNA (pre-miR-373) were transfected into PC-3 cells, E-cadherin expression was rapidly upgraded. The prerequisite of the miRNA maturation protein Dicer for the initiation of E-cadherin by pre-miR-373 was substantiated by knockdown probes Successive analysis showed that pre-miR-373 and miR-373 also smoothly promoted cold-shock domain-containing protein C2 (CSDC2), which has a apparent miR-373 target region in its promoter. In addition, tagging alone miR-373 transfection, improvement of RNA polymerase II was found at the promoters of both

CSDC2 and E-cadherin. Mismatch mutations to miR-373 proposed that the miR-373 sequence was exceptional for the gene induction. Transfection of dsRNAs specific to promoters presented that the simultaneous activation of E-cadherin and CSDC2 by miR-373 needed the miRNA target sites in both promoters (Place et al., 2008b).However, miR-373 is associated with the development of osteosarcoma, colorectal cancer, liver cancer, and breast cancer (Dong, Liao, He, Wu, et al., 2022) (Q. Chen, Li, Lu, Luo, Yang, et al., 2024) (Wei et al., 2015b).The involvement of miRNA-373 in urinary bladder cancer progression likely occurs through its promotion of epidermal growth factor receptor (EGFR) upregulation, thereby influencing EGFR-associated pathways governing cellular proliferation, migration, and invasion, and contributing to the malignant characteristics of bladder cancer cells (Wang et al., 2018d).

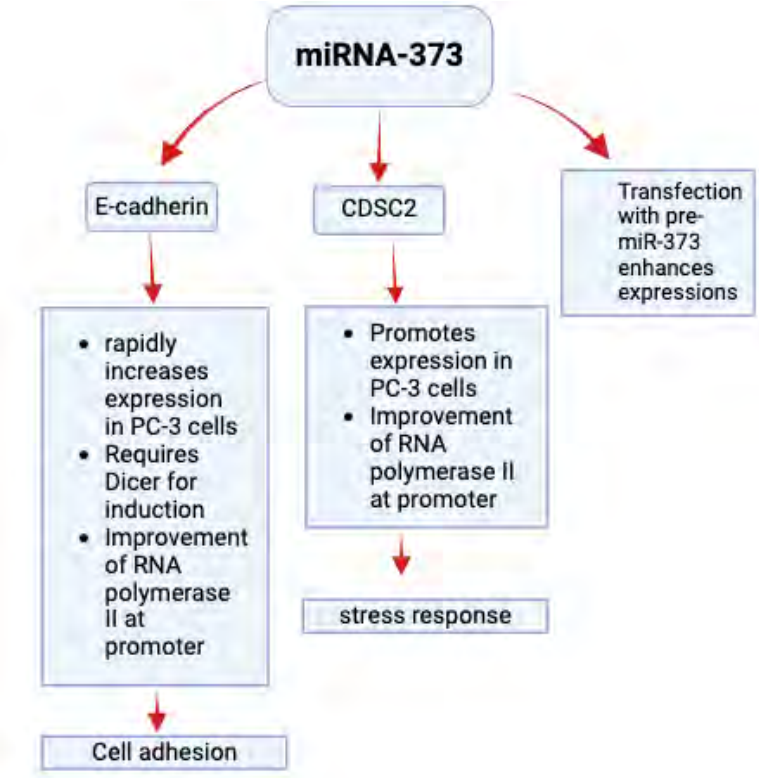

FIGURE 11. Schematic representation of the role of miR-373 in body

The connection between microRNA-155 (miR-155) and the evolving growth factor beta (TGF-β)/Smad pathway involves TGF-β, which controls important cell functions like growth and apoptosis. When the TGF-β pathway is activated, it activates Smad proteins that change how genes are expressed. This activation affects the levels of miR-155, which then influences other cell processes by controlling specific genes (Kong et al., 2008b). It has been proven that miR-155 expression stimulates monocyte precursors to dedicate to the macrophage lineage at the outlay of osteoclastogenesis. Pro-inflammatory signals, such as TNF-α and interferon-β (IFN-β), encourage the expression of miR-155 in the course of activation and differentiation of monocytic cells. Its overexpression obstructs the growth of osteoclasts in vitro. Particularly, it inhibits osteoclastogenesis in its early phases, before the precursors merge to shape multinucleated cells. The suppression of Mitf is the process by which miR-155 negatively affects osteoclastogenesis. OSCAR, cathepsin K and TRAP are three significant genes for osteoclast maturation and activities that are stimulated to convey by MITF. Furthermore, Socs1, a protein involved in cytokine signal transduction such as IFN-β, is blocked by miR-155. Repressing the harmful effects of pro-inflammatory cytokines on progenitor cell differentiation, SOCS1 assists osteoclastogenesis. Thus, miR-155 propels the outcomes of macrophages by downregulating genes participating in progenitor cell differentiation to osteoclastogenesis (*MicroRNA in Regenerative Medicine*, n.d.-b). Additionally, the miR-155 was relying on nuclear factor-κB (NF-κB). It was estimated that the NF-κB signaling pathway would be repressed by the high expression of miR-155 with a view to proficiently alleviate oxidative defect, inflammation, and apoptosis led on by IL-1β in rat nucleus pulposus cells. Furthermore, it was postulated that interrupting the expression of miR-155-5p may regulate the NF-κB signaling pathway to upregulate FNDC3B, encourage IL-1β-induced chondrocyte development, and minimize cell death. The miR-155/NF-κB signaling pathway was

selected to affect modification in inflammatory variables (J. Hu et al., 2022b). However, many classes of cancer, such as prostate, colorectal, lymphoma, breast and non-small cell lung cancer, show higher levels of miR-155 expression (M. Fawzy et al., 2023). MiR-155 regulates the GSK-3β/β-catenin pathway, subsequently influencing the growth and death of bladder cancer cells (Zc, D, et al., 2019).

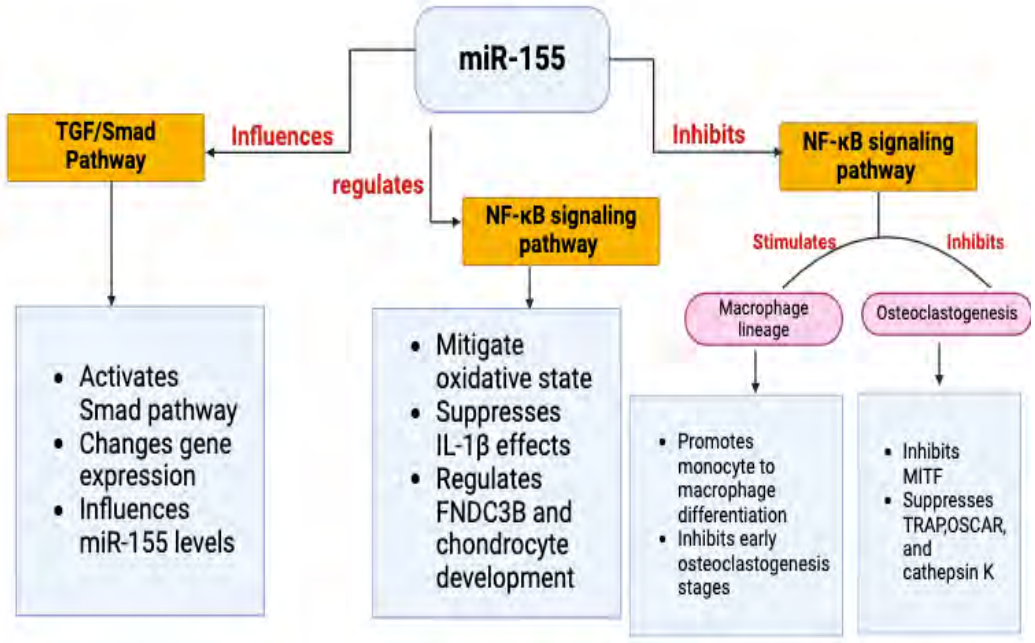

FIGURE 12. Schematic representation of the role of miR-155 in body

While microRNAs (miRNAs) show promise for cancer diagnosis, prognosis, and therapy, there are limitations to consider. Not all databases have been thoroughly explored, potentially impacting the comprehensiveness of the research. Additionally, population heterogeneity and variations in study design, interventions and sample usage can influence study outcomes, affecting the reliability of miRNA-based assays. The complexity of regulatory networks involving multiple miRNAs and their target genes poses challenges in understanding precise molecular mechanisms of cancer progression. Moreover, the absence of standardized protocols for miRNA detection and quantification complicates result interpretation across different studies. Furthermore, the analysis may result in publication bias since it is mainly relying on the standard, integrity and suitability of published material.Nonetheless, ongoing research efforts aimed at overcoming these obstacles may facilitate the clinical application of miRNA-based approaches in cancer management.

Conclusion

MicroRNAs (miRNAs) provide notable benefits in improving diagnostic rates and facilitating early identification of several diseases, including cancer, as they regulate gene expression patterns, contributing as promising biomarkers. Through our review, we've emphasized how miRNAs contribute to enhancing diagnostic and identification rates, supplying sensitive and specific indicators of disease presence and expansion. During assessing miRNA expression profiles in biological fluids and tissues, scientists have revealed an abundance of clinical findings that assists in accelerated and more accurate diagnosis. As sensitive and accurate biomarkers, miRNAs give insights on small variations in gene expression structure connected to the onset and progression of disease. Practitioners can detect abnormalities in advance by their capacity to perceive the complex

molecular markers of diseases, which facilitates for on time interventions and individualized treatment schemes. Furthermore, predictive evidence from miRNA detection tests has shown likelihood in aiding in the presumption of therapy results and illness outcomes. The implementation of miRNA-based analyses in clinical trials has huge prospect to evolve diagnostic procedures and, in the end, improve patient outcomes as long as active research efforts resume to flourish detection strategies and widen biomarker discovery initiatives. Thus, studying miRNA expression profiles in bodily fluids and tissues, researchers have gained higher diagnostic precision and earlier detection of cancers, aiding timely therapeutic interventions and personalized treatment strategies. With ongoing research and technological advancements, integrating miRNA-based assays into clinical practice holds great potential for enhancing disease management and patient outcomes. Efforts to standardize protocols, expand biomarker discovery, and improve data analysis will be essential for maximizing the clinical utility of miRNAs in diagnostic settings. Additionally, in order to find novel therapeutic targets and improve current treatment modalities, more investigation into the underlying molecular pathways of cancer is necessary. This entails investigating the part that genetic mutations, epigenetic modifications, and microRNAs play in the etiology of bladder cancer. Furthermore, the accuracy of bladder cancer diagnosis and staging can be improved by incorporating cutting-edge imaging modalities like molecular imaging and multiparametric MRI into standard clinical practice. Standardization of diagnostic procedures and techniques is also essential to guarantee dependability and uniformity between healthcare facilities. In order to expedite the translation of promising diagnostic and prognostic tools from bench to bedside, researchers, physicians, and industry partners must work together. Finally, patient education and awareness initiatives can be extremely important for advancing early

detection and encouraging individuals to seek medical attention promptly for symptoms suggestive of bladder cancer, ultimately improving patient outcomes and survival rates.

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