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REVIEW

A Fingerprint of miRNA-93 in Cancer Progression and Therapeutic Targets

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Abstract

MicroRNAs (miRNAs) are small non-coding ribonucleic acids (RNAs) that can greatly influence cellular activity by interacting with mRNAs either individually or through RISC. This wide range of activity shown by miRNAs makes them highly sensitive, and any dysfunction on their part can cause many diseases, including cancer. MiR-93 is one such miRNA that has been found to be associated with various types of cancers, including hepatocellular carcinoma, breast cancer, gastric cancer, and lung cancer. This review article focuses on the role played by miR-93 in several common cancers to shed more light on miRNA and its association with cancer. The article discusses the oncogenic or tumour-suppressing function of miR-93 in different types of cancers and elucidates the various pathways through which miR-93 exerts its oncogenic or tumour-suppressing activities. The article also highlights potential therapeutic targets that can be developed based on the understanding of the underlying mechanism of cancer and the role of miRNAs in this disease.

Keywords: microRNA-93 (miRNA-93)- carcinoma- target genes- regulatory mechanisms- therapeutic targets

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Introduction

The genetic material of cells consists of ribonucleic acids (RNAs) and DNA. RNAs can be broadly divided into two groups: non-coding RNAs, which mostly play regulatory roles and do not translate, and coding RNAs, which are involved in the creation of proteins through translation. Non-coding RNAs include, but are not limited to, miRNAs, siRNAs, piRNAs, snoRNAs, and snRNAs [1]. MiRNAs or miRs are small, single-stranded, non-coding RNAs that are 21 to 23 bp long and are found in most life forms, including animals, plants, and viruses. These RNAs are usually active in the post-translational regulation of cellular activity through interaction with other RNAs, mRNA [2, 3]. miRs can function individually or as a part of the RNA-induced silencing complex (RISC) [2]. During miRNA biogenesis, DNA is transcribed into pri-miRNA, which is processed into pre-miRNA by endoribonuclease Drosha. These pre-miRNAs are then transported to the cytoplasm and are cut into correct-sized miRs, upon which these miRs can act individually or join RISC (Figure 1) [4]. This review will mainly focus on miR-93, a miRNA that is coded from the 7q22.1 region and is a member of the pro-oncogenic miRNA-106b-25 cluster. Studies have shown that miR-93 is involved in cellular proliferation and cell cycle progression [5]. This review will mainly focus on miR-93, a miRNA coded from the 7q22.1 region and is a member of the pro-oncogenic miRNA-106b-25 cluster. Studies have shown that miR-93 is involved in cellular proliferation and cell cycle progression [6]. It has also been linked to other diseases like osteoarthritis, rheumatoid arthritis, atherosclerosis, hepatic injury, Parkinson's disease, acute myocardial infarction, and chronic kidney disease [6].

Breast cancer

Breast cancer is one of the most commonly diagnosed cancers in the world. It is the first or second most diagnosed cancer among women, depending on the area, especially in modern countries. It is also the second leading cause of cancer deaths among women after lung cancer. Multiple polymorphisms and preventable environmental factors

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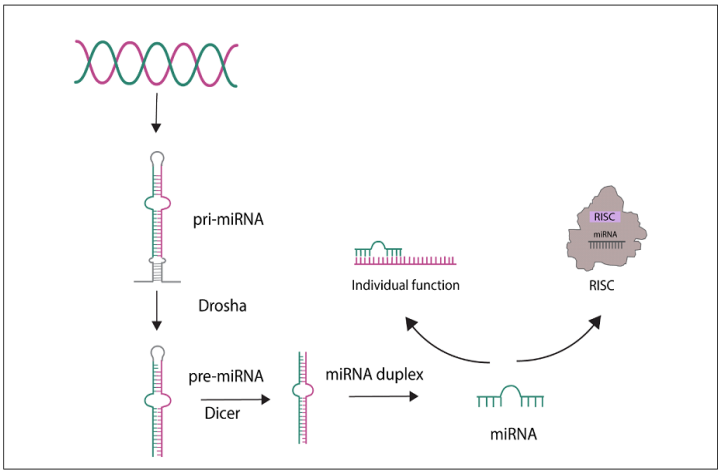

Figure 1. Schematic Illustration of microRNA Biogenesis. The biogenesis of miRNA starts by generating a long hairpin structure (pri-miRNA) which is cleaved by an enzyme called Drosha generating short hairpin called pre-miRNA. This is again cleaved by an enzyme called Dicer to release RNA duplicate of 22 nucleotides. The double stranded miRNA associated with the RNA induced silencing complex (RISC) leads to unwind the miRNA and becomes a functional miRNA

such as excess body weight, physical inactivity, and alcohol intake are among the risk factors for this disease [7-10].

Nana Li et al. conducted a study on breast cancer cell lines, MDA-MB-231 and MCF-7, compared to normal breast cells MCF-10A. The study reported high levels of miR-93 in cancer cells as compared to normal cells. This upregulation was associated with an increased activity of the phosphatidylinositol-3 kinase (PI3K)/Akt pathway, a vital pathway that is crucial for regulating cell growth, motility, survival, metabolism, and angiogenesis and can cause cancer if misregulated [11, 12]. This upregulation was responsible for the migration and invasion of BC cells, which can in turn cause metastasis. Upregulation of PTEN was able to reverse the effects of miR-93 upregulation in these cancer cells [12]. Another study reported an increase in miR-93 in ductal carcinoma in situ (DCIS) breast cancer patients after comparing the miR-93 expressions in 42 DCIS patients with those in 39 healthy women [13].

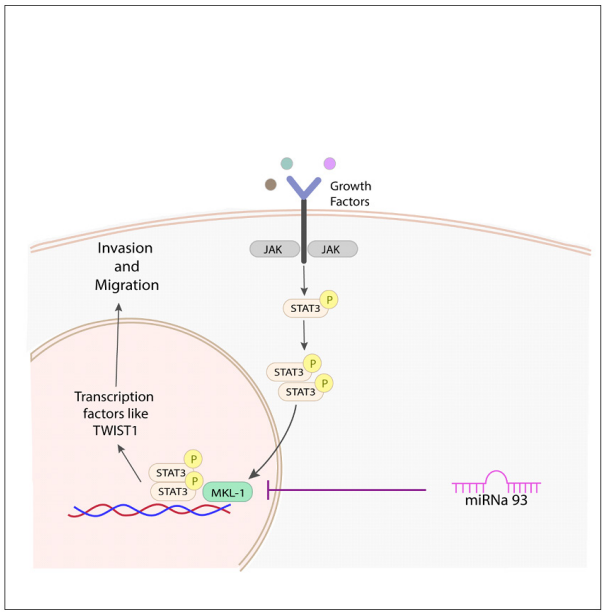

Figure 2. Process of EMT Through STAT/MKL-1 Axis and Inhibitory Effect of miRNA. JAK (Janus Kinase) mediate phosphorylation of STAT (signal transducer and activator of transcription) which can homo dimerized and translocate into nucleus thereby it can bind to MKL-1 together promote EMT genes to affect breast cancer migration. miR-93inhibits the EMT of breast cancer cells through suppressing the expression of MKL-1 and STAT3.

Considering this, it is necessary to note that one study reported that miR-93 could inhibit the process of epithelial–mesenchymal transition (EMT) in BC cells. EMT is a process in which cells lose their adhesion and gain invasive properties associated with the mesenchymal cell. This process can often be seen in cancer tissues and is a major cause of metastasis (Figure 2). The study claimed that miR-93 can bind to the 3'UTR of MKL-1 and STAT mRNAs, two major components of EMT, and inhibit EMT, thus reducing the invasiveness and progression of BC [14, 15]. By comparing the results from these studies, we can determine that due to the importance and wide range activity of miR-93, it has been studied extensively in correlation with multiple diseases, including breast cancer.

Colorectal cancer

Colorectal cancer is one of the most common cancers worldwide, affecting both men and women. It is more prevalent in modern countries than in developing countries, and it is the second leading cause of cancer-related deaths among both women and men in Western countries. Several risk factors have been identified for colorectal cancer, including preventable conditions such as smoking, fat-rich diets, high alcohol intake, physical inactivity, and severely high body weight [16, 17].

A recent study conducted on the SW480 colorectal cancer cell line reported that treating these cells with miR-93 mimic led to a reduction in the p-PI3K/PI3K and p-AKT/AKT ratio, thus suppressing progression, invasion, and migration while increasing apoptosis in colorectal cancer cells [2]. It has also been reported that miR-93 can inhibit the invasion, migration, and proliferation of colon

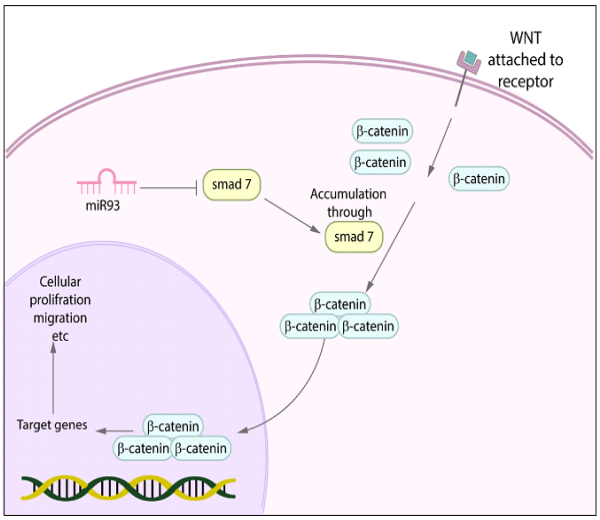

Figure 3. Inhibition of Wnt/β-catenin Pathway Through miR93 Regulation of Wnt/β-catenin Signaling by miRNA93. Left panel: miRNA93 targeting inactive Wnt/β-catenin signaling to initiate EMT. In the absence of mRNA93, β-catenin is phosphorylated by GSK3β by forming a destruction complex with Axin, APC, CKIα and GSK3β, forming β-catenin degradation by ubiquitin. MiRNAs facilitate EMT by targeting Wnt/β-catenin suppressors. Right panel: miRNAs targeting activated Wnt/β-catenin signaling to inhibit EMT.

carcinoma cells. Reportedly, miR-93 can downregulate smad7 by binding to its 3'UTR, thus prohibiting β-catenin accumulation and suppressing the Wnt/β-catenin pathway, which stops tumour progression (Figure 3) [18]. Yingqiang Liu et al. concluded that HOTAIR lncRNA knockdown can increase miR-93 expression, since HOTAIR acts as a sponge for miR-93; this can in turn inhibit ATG12 activity, thereby increasing radiosensitivity and apoptosis in colorectal cancer cells [19]. It has been shown that lncRNA CA3-AS1 can inhibit proliferation invasion and apoptosis in CRC cells. Studies have shown that miR-93 can bind to lncRNA and inhibit its activity. miR-93 can also inhibit PTEN tumour suppressor activity and regulate CRC progression [20]. It is important to note that miR-93 can either stop or help CRC progression depending on which activity it exerts. Depending on its interaction, it can inhibit or promote CRC progression and invasion.

Lung cancer

Lung cancer is the most common type of cancer among both men and women in most countries, including the United States. It is also the leading cause of cancer-related deaths among men and the second leading cause among women. Lung cancer accounts for 12.4% of new cancer cases each year and 17.6% of cancer-related deaths annually. Genetic susceptibility, poor diet, occupational exposure, and air pollution are among the risk factors for this disease [21-23].

Studies on small cell lung cancer (SCLC) have shown that these cells have increased expression of miR-93. This miRNA then represses the expression of smad7 and p21, leading to the activation of the transforming growth factor-β (TGF-β) pathway and resulting in EMT. Circular RNA epithelial splicing regulatory protein-1 (cESRP1) can reportedly reverse this effect by sponging miR-93 (Figure 4) [24]. Other studies have also seen a correlation between miR-93 and non-small cell lung cancer (NSCLC), where the expression of miR-93 is usually elevated in NSCLC tissue [25]. Reportedly, miR-93 not only shows an association with NSCLC but also binds to tumour-suppressors PTEN and RB1 mRNA, repressing their expression and helping cancer progression. MiR-93 upregulation has also been heavily correlated with poor prognosis and low survival rates [26]. Another way that miR-93 can manipulate the TGF-β pathway in lung cancer is by binding to 3'UTR of NEDD4L mRNA and repressing its expression. NEDD4L can downregulate the TGF-β pathway through interaction with smads, especially smad2 [27]. MiR-93 can also bind to 3'UTR of DAB2 mRNA and inhibit its expression. Downregulation of DAB2 is highly correlated with miR-93 overexpression and poor prognosis and survival rate of lung cancer patients. The full mechanism of DAB2 activity is not known; however, DAB2 overexpression in in vitro specimens strongly inhibits cellular growth and proliferation of lung cancer cells [28]. LKB1 tumour suppressor is no exception to the inhibitory effect of miR-93. MiR-93 can bind to the 3'UTR of LKB1 mRNA and inhibit its expression. The combined inhibition of LKB1, PTEN, and p21 through miR-93 can also initiate the PI3K/Akt pathway and promote invasion, migration, and metastasis of lung cancer [29]. Thioredoxin-1 (Trx-1) binding protein-2 (TBP-2) can also be downregulated by miR-93. TBP-2 can regulate oxidative stress and inhibit cellular proliferation while promoting apoptosis. This protein is usually downregulated in cancer tissue, and in some studies, this decrease was correlated with miR-93 expression. MiR-93 knockdown usually increases the expression of TBP-2, which can inhibit cancer progression [30]. Reportedly, this is also heavily correlated with poor prognosis and survival in lung cancer patients [31]. Owing to these reports, it can be assumed that miR-93 mostly helps the progression of lung cancer through its many activities.

MiR-93 in cancer diagnosis and prognosis

Despite advances in early cancer detection, the majority of cancers are still detected at an advanced stage. As a result, the discovery of novel diagnostic biomarkers and treatment strategies is critical to the control of most cancers. As a key member of the miRNA-106b-25 cluster, miR-93 has emerged as a promising biomarker due to its dysregulation in various cancer types, including colorectal, prostate, lung, and breast cancers [11, 12, 32, 33]. Understanding the detailed mechanisms through which miR-93 influences tumorigenesis and progression offers a promising path for establishing novel diagnostic tools and prognostic indicators in the battle against cancer.

MiR-93 plays a significant role in both physiological and pathological conditions, particularly in diseases like cancer [34]. We previously mentioned that numerous studies have explored the regulation of miR-93, demonstrating its downregulation or upregulation across various cancer types. Studies by Li, Danielsen, and their colleagues [11, 12] have highlighted the crucial role of

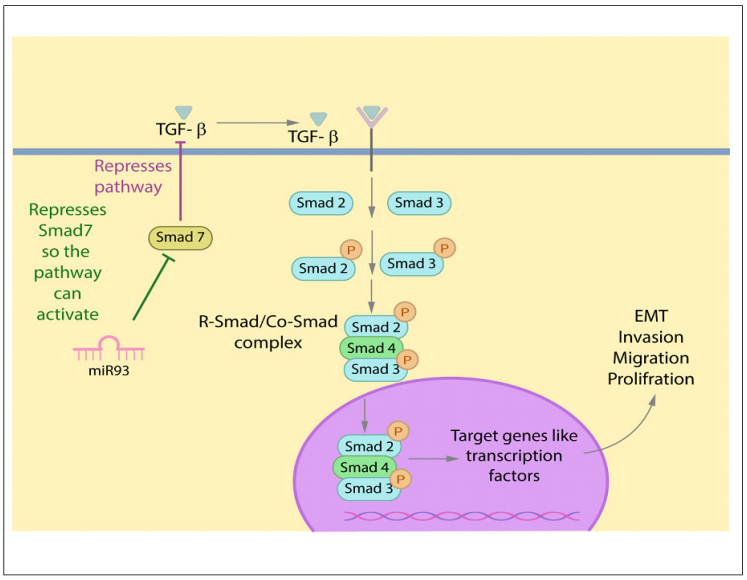

Figure 4. Role of miR93 in Keeping TGF-β Pathway Active through Inhibiting Smad7 Activity

miR-93 in modulating key oncogenic pathways such as the PI3K/AKT pathways, shedding light on its significance in cancer pathogenesis and its potential as a therapeutic target. Likewise, Ni and his colleagues showed that in DCIS breast cancer patients, miRNA-93 is highly elevated in patients than in healthy women [13]. Their findings suggest that assessing the abnormal expression of miR-93 in BC patients may have clinical utility, especially in the diagnosis and prognosis of BC. Furthermore, the correlation between aberrant miR-93 expression levels and clinicopathological parameters, including the tumour stage, metastasis, and patient survival rates underscores its utility as a prognostic marker of various types of cancer [19]. Additional study is required to determine the clinical feasibility of these strategies and have a greater awareness of miRNA-93's involvement in both malignant and non-malignant disorders [6]. MiR-93 thus holds promise as a diagnostic biomarker and prognostic indicator of cancer.

MiRNA-based therapeutic approaches

MiRNA-based therapeutic approaches represent a promising avenue in the field of molecular medicine, offering innovative strategies for the treatment of various diseases, particularly cancer. The expression of many genes that code for proteins is likely influenced by miRNAs, one of the most common forms of gene regulatory molecules in multicellular organisms [35]. MiRNAs, which are small non-coding RNA molecules, play critical roles in several biological processes and disease pathways, including cancer, due to their dysregulated expression patterns in various cancer types [36]. Consequently, targeting dysregulated miRNAs holds significant therapeutic potential. MiRNAs are divided into two categories in cancer: tumour-suppressive and oncogenic [37]. Abnormal miRNA expression patterns, either downregulated or upregulated, have been identified in a wide range of human malignant tumours, including lymphoma, breast cancer, colorectal cancer, prostate cancer, and glioma [33]. A subset of miRNAs, including miR-9, miR-10b, miR-17, miR-21, miR-132, miR-155, miR-222, miR-375, and miR-519a, has been identified as oncogenes (oncomiRs), which are actively involved in the etiology and development of malignant neoplasms [38]. MiRNA expression patterns can give valuable clinical information regarding a patient's prognosis, particularly across cancer types. For instance, in lung cancer, low levels of the let-7 miRNA family and high levels of miR-155 are linked to a bad prognosis [39, 40]. The motivation for modulating miRNA expression in disease tissues lies in the discovery that tumour-suppressive miRNAs (TS-miRNAs) are more numerous or functional in normal tissues, whereas oncogenic miRNAs (onco-miRNAs) are upregulated and activated mainly in tumour tissues. This contrast forms the basis for targeted therapeutic interventions aimed at restoring normal miRNA levels or inhibiting onco-miRNA activity to treat diseases such as cancer [41]. Some miRNAs play two roles, serving as a tumour suppressor in one cancer type and an oncomiR in another. MiR-10b, for example, functions as an oncomiR in glioblastoma (GBM) by targeting genes such as p21, p16, BIM, and TFAP2C; however, its downregulation in cervical cancer, gastric cancer, and small cell carcinoma supports a tumour-suppressive role [42].

The therapeutic application of miRNAs involves two strategies. MiRNA Replacement Therapy: This approach involves the introduction of synthetic miRNA mimics to restore the expression and function of downregulated or lost miRNAs in diseased cells. These mimics are designed to mimic the endogenous miRNA sequence and function; for instance, restoring TS-miRNAs, such as miR-34, has shown promise in inhibiting proliferation, inducing apoptosis, and suppressing metastasis in various cancer types [43]. Inhibition of miRNAs oncogenic (gain-of-function strategy) Therapy: This strategy seeks to inhibit the overabundance or abnormal activity of oncogenic miRNAs, which contribute to tumour growth [44]. The techniques utilised in this strategy include

using: a. miRNA antagonists (anti-miRs), which are oligonucleotides that bind selectively to oncogenic miRNAs, preventing them from attaching to their target mRNA molecules, b. Locked Nucleic Acids, which are modified nucleotides that improve the stability and binding affinity of anti-miRs to their target miRNAs, hence increasing their efficacy, c. antagomiRs, which like anti-miRs, are synthetic oligonucleotides that bind to complementary regions in certain miRNAs, limiting their action, and d. Small-Molecule Inhibitors, which are chemical compounds designed to impair the action of certain miRNAs, providing an alternate method for inhibiting miRNA function [45].

The delivery of miRNA mimics or antagomirs offers various challenges that must be solved for effective therapeutic application [46]. Nucleases can swiftly break down these molecules, and they may be removed from circulation, reducing their bioavailability. Furthermore, concerns including immunotoxicity and limited tissue permeability hamper their administration. Researchers are currently investigating new delivery techniques, such as nanoparticle-based systems, viral vectors, and chemical modifications, to improve the stability and target specificity while reducing side effects. Despite these obstacles, the promise of miRNA-based therapeutics in treating a variety of disorders remains attractive, prompting more study in this area [47, 48].

Apart from systemic applications such as injection and infusion, other methods for miRNA-based drug delivery are emerging, such as implantable 3D matrices, inhalation devices, and food intake. Combining miRNA therapies with chemical modifications, biomolecule conjugation, or carriers results in more effective and site-specific cell targeting. To decrease off-target effects and avoid miRNA overload, a complete risk assessment of miRNA therapeutics is required before any in vivo targeting [41]. Given that miRNA-based treatments hold great promise for improving patient outcomes and quality of life worldwide, their development is expected to substantially impact medicine in the future.

In conclusion, MicroRNAs(miRNAs) are small non-coding RNAs that can greatly influence cellular activity by interacting with mRNAs either individually or through RISC. This wide range of activity shown by miRNAs makes them highly sensitive, and any dysfunction on their part can cause many diseases, including cancer. MiRNA activity can be an oncogenic or tumour-suppressing factor in cancer. We have mentioned various pathways through which miRNAs are able to exert their oncogenic or tumour-suppressing activities in breast, colorectal, and lung cancers. Understanding the underlying mechanism of cancer and the role of miRNAs in this disease can open up new therapeutic horizons, broaden our understanding of this disease, and help us prevent and treat patients suffering from this disease.

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Statement of Transparency and Principles:

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• The study data are available upon reasonable request.

• All authors contributed to the implementation of this research.

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