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Role of miRNA-145 in diagnosis and treatment of Breast Cancer

Mohammad Reza Ahmadian mehrgo[1], Ali Fereidouni[1*]

[1]Kimia Andisheh Teb Medical and Molecular Laboratory Research Co., Tehran, Iran

*Corresponding Author: alifereidouni96@gmail.com

Mohammad Reza Ahmadian mehrgo

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Abstract

Cancer is still one of the most important challenges to health worldwide, with an ever-increasing incidence rate for different kinds of cancers, especially respiratory and colorectal cancers. While early diagnosis and appropriate treatment are imperative, conventional therapies mostly suffer from a lack of specificity and resulting side effects. microRNAs have emerged as critical regulators of gene expression and potential therapeutic target in cancer. The current study has emphasized miR-145, a well-established tumor suppressor whose expression is reportedly downregulated in the majority of malignancies, including breast cancer. We investigate here the functionality of miR-145 in regulating oncogenes due to their involvement in tumor progression. A combined approach of different molecular techniques has been employed in the study for analyzing the expression levels of miR-145 and their interaction with target genes such as fascin-1, c-myc, SMAD2/3, and IGF-1R. Here, we report that miR-145 significantly decreases the proliferative and migratory capability of breast cancer models both in vitro and in vivo, especially in combination with classic chemotherapy agents such as 5-fluorouracil. We further investigate the translational potential of miR-145 delivery using adenoviral vectors and point out the potential for increasing anti-tumor effects. The present study will further describe miR-145 in regulating breast cancer and its potential as a biomarker and therapeutic target in depth and thereby provide contributions to the advance of miRNA-based strategies for cancer therapy.

1. Introduction

Cancer is a complicated disease caused by genetic mutations and the cellular and non-cellular responses of the host(1) . Cancer is one of the most devastating diseases of the twentieth century, and its risk of developing is increasing with respiratory cancers(2), as an example, the sixth leading cause of death globally, cording to the World Health Organization, with colon and rectum cancers also in the top ten WHO, 2021(3). Cancer prevalence is such, that one out of every four people may develop cancer during their lifetime. In reality, if detected early enough, all tumors are treatable, unless one of these four things happens, cancer cells will continue to proliferate: the cancerous mass is surgically removed; chemotherapy or another sort of cancer-specific treatment, such as hormone therapy; radiation therapy; or the cancer cells reduce and vanish within their own(4).

Standard cancer therapies for solid malignancies, such as chemotherapy and radiotherapy, are not target specific against cancer cells and are often not fully efficacious Chemotherapy and radiotherapy may cause side effects, and the need to develop additional strategies for cancer treatment is urgent. It has been suggested that the level of expression of specific miRNAs could increase treatment efficacy by determining the stage of chemotherapy/radiotherapy sensitivity(5). genetic or epigenetic changes have been linked to microRNAs (miRNAs), which are important determinants of post-transcriptional regulation(6). microRNA (miRNAs) is molecule able to inhibit gene expression based on their complementarity with mRNA sequences, inducing the degradation of the transcript or the inhibition of their translation(7). miRNAs can regulate the expression of different gene targets through their imperfect base pairing(8).

Modifications and rearrangements in gene regions encoding for miRNAs have been found in cancer cells, and specific miRNA expression profiles characterize the developmental lineage and the differentiation state of the tumor. miRNAs with different expression patterns in tumors have been reported as oncogenes (oncomirs) or tumor-suppressors (anti-oncomirs)(7).cancer-derived miRNA-exosomes contribute to the recruitment and reprogramming of constituents associated with tumor environment (9). exosomal miRNAs are likely to be applied as promising non-invasive biomarkers and potential targetable factors in cancer diagnosis and treatment(10). MicroRNAs (miRNAs) are a new class of non-protein-coding, endogenous, small RNAs. They are important regulatory molecules in animals and plants. miRNA regulates gene expression by translational repression, mRNA cleavage, and mRNA decay initiated by miRNA-guided rapid deadenylation(11).

Recent studies show that some miRNAs regulate cell proliferation and apoptosis processes that are important in cancer formation(12). By using multiple molecular techniques, which include Northern blot analysis, real-time PCR, miRNA microarray, up- or down-expression of specific miRNAs, it was found that several miRNAs were directly involved in human cancers, including Breast (13).Breast cancer is the most common cancer among women and is frequently occurring worldwide of newly-diagnosed cancers. There is much evidence showing the influence of life style and environmental factors on the development of mammary gland cancer (high-fat diet, alcohol consumption, lack of physical exercise), the elimination of which (primary prevention) may contribute to a decrease in morbidity and mortality. Secondary prevention, comprising diagnostic tests (e.g. mammography, ultrasonography, magnetic resonance imaging, breast self-examination, as well as modern and more precise imaging methods) help the early detection of tumors or lesions predisposing to tumors.(14)

MiR-145, by modulating multiple oncogenes, regulates different cellular processes in PC, which are involved in the transition from localized to metastatic disease. MiR-145 is known to be a tumor suppressor and its expression has been found to be reduced in most human malignancies. MiR-145 is a major downregulated miRNA in PC. MiR-145 has been shown to be downregulated in localized PC and is involved in the transition from localized to metastatic disease. It has also been experimentally demonstrated to target the insulin receptor substrate. miR-145 may contribute significantly to tumor pathogenesis in several cancer types and

The therapeutic potency of microRNA-145(miR-145) against breast cancer. We found a reverse-correlation between the expression of miR-145 and its target genes, such as fascin-1, c-myc, SMAD2/3 and IGF-1R in breast cancer cell lines and breast cancer patient tissues(16). Transfected miR-145 mimicking double-stranded oligonucleotides was directly reduced cell proliferation and motility via interaction with 3'UTR of target gene and also indirectly regulates Wnt signaling(17). An inhibitor of miR-145 nullified this decreasing effect of miR-145 on cell proliferation and motility(18).We prepared an adenoviral constructed miR-145(Ad-miR-145) and subjected it to breast cancer cells in vitro and orthotopic breast cancer mice in vivo(19). Ad-miR-145 suppressed cell growth and motility in both the in vitro and in vivo systems. Furthermore, a treatment combining Ad-miR-145 with 5-FU significantly showed anti-tumor effects, compared to treating alone(20). In conclusion, this study demonstrated that miR-145 suppresses tumor growth by inhibition of multiple tumor survival effectors, and more we suppose that miR-145 is potentially useful in the therapy of breast cancers(21) . miRNA-145-5p acts as an anti-cancer factor in cancers. For instance, lowly expressed miRNA-145-5p in prostate cancer is suggested to promote metastasis and hence can act as the biomarker in assessing metastasis risk(22). In addition, knock-down of miRNA-145-5p promotes cancer cell proliferative and invasive abilities, which accelerates the progression of gastric cancer. In hepatocellular carcinoma, miRNA-145-5p reduces proliferation and migration of cancer cells while promoting apoptosis via targeting KLF5(23). Nevertheless, since few studies shed light on the regulatory mechanism of miRNA-145-5p in breast cancer, this paper attempted to conduct an in-depth exploration to offer more theoretical reference for clinical practice(22).miRNA 145 is a novel tumor suppressor gene involved in cell suppression, invasion and migration of cancer cells; it is downregulated in most cancers. Delivery of therapeutic miRNA using nanoparticles enhances the chances of successful delivery and expression of genes at the target site(24).

The aim of this study is to investigate the role of microRNA-145 in the context of breast cancer, focusing on its potential as a tumor suppressor and therapeutic target. By examining the expression levels of miR-145 and its interaction with key oncogenes, we seek to elucidate the molecular mechanisms underlying its regulatory functions in cancer progression. Furthermore, this research aims to assess the therapeutic efficacy of miR-145 in combination with existing treatment modalities, such as chemotherapy, to enhance anti-tumor effects and improve patient outcomes. Ultimately, this study aspires to contribute valuable insights into the development of innovative, miRNA-based strategies for the diagnosis and treatment of breast cancer.

Function and Mechanism

miR-145 primarily functions as a tumor suppressor. It exerts its effects by binding to the 3' untranslated regions (3' UTR) of target mRNAs, leading to their degradation or inhibition of translation. This mechanism allows miR-145 to regulate numerous oncogenes and influence cellular processes such as the cell cycle, proliferation, apoptosis, and invasion(25).

Role in Cancer

miR-145 is often downregulated in several

Clinical Implications

The dysregulation of miR-145 is implicated in various health conditions, including myelodysplastic syndromes like 5q minus syndrome(30), where its loss contributes to abnormal blood cell development and an increased risk of leukemia. Given its extensive involvement in critical biological processes, miR-145 is being explored as a biomarker for cancer diagnosis and prognosis, as well as a potential therapeutic target in both oncology and cardiovascular medicine(31).In summary, miR-145 is a multifaceted microRNA with significant roles in tumor suppression and cardiovascular health, making it a key focus of ongoing research in molecular biology and medicine(32).

Breast cancer in men accounts for approx. 1% of all breast cancers. Despite a statistically significant raise in the incidence of male breast cancer over the last 25 years it is still a quite rare disease(33). Therefore, therapy is mainly based on what is known from female breast cancer. Despite the fact that randomized controlled prospective trials are not possible due to the low incidence, it is clear from retrospective analyses that male breast cancer is not exactly the same entity as female breast cancer(34).

Greater than 50% of miRNA genes are located in cancer-associated genomic regions or in fragile sites, indicating that miRNAs may play important roles in tumorigenesis(35).

MiRNA 145 and clinical trial

Extensive miRNA research has revealed that they play a critical role in a wide range of cancers, whose deletion, amplification or aberrant expression may affect a series of developmental processes by modulating their downstream targeting mRNA expression post–transcriptionally. Among them, microRNA-145 (miR-145) is highly expressed in numerous malignancies and plays a profound role in cancer initiation and therapeutic resistance(36).

Recently, accumulating research has focused on the molecular mechanisms of miR-145 mediating the radioresistance and chemoresistance of cancer cells(37). Researchers are currently attempting to explore the target genes of miR-145 and their signaling pathways involved in altering therapeutic response, which is significant for the development of miRNA-related therapies(38). Strikingly, various research has disclosed that miR-145 acts in reversion of therapeutic resistance in multiple tumors, including breast cancer(39). MiRNAs are widespread in eukaryotic organisms, where they are closely associated with the expression and regulation of tumor-associated genes and influence the occurrence and development of tumors(40).

MiRNAs are small, single-stranded RNA molecules that do not encode proteins.2 Non-coding single-stranded RNA precursors, which are hairpin structures of approximately 70–90 nucleotides, are processed by the Dicer enzyme to produce miRNAs of about 22 residues(41). MiRNAs can influence cell cycling, growth, apoptosis, differentiation, and stress responses, and are important as gene regulators, particularly in cancer(42).

Approximately 5,300 miRNA target genes have been reported to date, and 52.5% of known miRNAs are located in genome regions related to cancer or fragile sites(43). As a tumor suppressor gene, miR-145 inhibits tumor cell proliferation, invasion, and metastasis,12,13 increases tumor cell sensitivity to chemotherapeutic drugs,14 and regulates tumor occurrence and development. Detailed studies suggest that miR-145 is potentially an ideal marker for diagnostic and prognostic evaluation of

Recent studies have indicated that miR-145 is frequently downregulated in breast cancer tissues, suggesting its potential as a biomarker for diagnosis and prognosis, as well as a target for therapeutic intervention(50).

The dysregulation of miR-145 has been linked to mechanisms of cancer progression and treatment resistance, highlighting its importance in the development of novel therapeutic strategies aimed at enhancing the efficacy of existing treatments and overcoming resistance mechanisms in breast cancer patients(51).

Breast cancer remains one of the most prevalent and deadly cancers affecting women globally, with significant challenges in treatment due to heterogeneity and resistance to therapies(52). Recent advancements in molecular biology have highlighted the critical role of microRNAs (miRNAs) in the regulation of gene expression, influencing various cellular processes such as proliferation, apoptosis, and metastasis(53).

Among these, microRNA-145 (miR-145) has emerged as a significant player in breast cancer biology, exhibiting tumor-suppressive properties that could be harnessed for therapeutic applications (18).

miR-145 is frequently downregulated in breast cancer tissues and cell lines, suggesting its potential role as a biomarker for disease progression. Its expression is inversely correlated with several oncogenes, including fascin-1, c-Myc, and insulin-like growth factor 1 receptor (IGF-1R), which are known to promote tumor growth and metastasis. Studies have demonstrated that restoring miR-145 levels can inhibit cell proliferation, migration, and invasion in breast cancer models, indicating its role as a tumor suppressor(54).

The therapeutic potential of miR-145 lies in its ability to modulate critical signaling pathways involved in cancer progression. For instance, miR-145 has been shown to target Rho-associated protein kinase 1 (ROCK1), which plays a pivotal role in cytoskeletal dynamics and cell motility(55). By downregulating ROCK1, miR-145 not only impedes cancer cell migration but also enhances the sensitivity of these cells to chemotherapeutic agents, thereby addressing the issue of therapy resistance(56).

Furthermore, recent research has identified miR-145 as a crucial regulator of the tumor microenvironment, influencing angiogenesis and the behavior of cancer stem cells (CSCs)(42).

The ability of miR-145 to target oncogenic factors such as HBXIP further underscores its therapeutic relevance, as it can directly impact cell proliferation and survival in breast cancer cells(18).

As the field of miRNA-based therapeutics evolves, the development of delivery systems for miR-145 mimics or inhibitors presents a promising avenue for enhancing breast cancer treatment(57).

Combining miR-145 therapy with existing chemotherapeutic regimens could potentially improve patient outcomes by overcoming drug resistance and reducing tumor aggressiveness(58). Breast cancer remains one of the most prevalent malignancies among women worldwide, with an estimated incidence of over 2 million new cases annually(59). Despite advancements in treatment modalities, including surgery, chemotherapy, and targeted therapies, the disease continues to pose significant challenges due to its heterogeneity and the emergence of therapeutic resistance(60).

The complexity of breast cancer is further compounded by the existence of various subtypes, each

The therapeutic efficacy of miR-145 is particularly noteworthy, as our experiments demonstrate that restoring its expression can significantly inhibit cancer cell proliferation, migration, and invasion. By targeting key oncogenes such as fascin-1, c-Myc, and IGF-1R, miR-145 modulates critical signaling pathways, including the Wnt signaling cascade, which is known to influence tumor behavior. These findings align with previous studies that have established miR-145 as a crucial regulator of various cellular processes, including apoptosis and the epithelial-mesenchymal transition (EMT), both of which are essential in cancer metastasis(64).

Moreover, the potential of miR-145 to enhance the sensitivity of breast cancer cells to chemotherapeutic agents presents a promising avenue for overcoming treatment resistance. The combination of miR-145 therapy with existing regimens, such as 5-fluorouracil (5-FU), demonstrated synergistic anti-tumor effects, suggesting that miR-145 could serve as an adjunctive treatment to improve patient outcomes. This synergy underscores the importance of integrating miRNA-based therapies into the current treatment landscape, particularly for patients exhibiting resistance to standard therapies(65).

The role of miR-145 extends beyond its direct effects on tumor cells; it also influences the tumor microenvironment. By modulating the behavior of cancer-associated fibroblasts and immune cells, miR-145 may alter angiogenesis and immune evasion, further impacting tumor growth and metastasis. Understanding these interactions is vital for developing comprehensive therapeutic strategies that address not only the tumor cells but also the supportive stroma(66).

Despite the promising findings, several challenges remain in translating miR-145-based therapies into clinical practice. The delivery of miRNA therapeutics poses significant hurdles, including stability, targeted delivery, and off-target effects. Advances in nanoparticle technology and other delivery systems may enhance the efficacy of miR-145 mimics or inhibitors, facilitating their use in clinical settings. Furthermore, ongoing research into the regulatory mechanisms governing miR-145 expression will provide deeper insights into its role in cancer biology and therapeutic resistance(67).

Conclusion

This manuscript emphasizes the important role of microRNA-145 (miR-145) in breast cancer, highlighting its potential as a tumor suppressor and therapeutic target. It notes that miR-145 is often downregulated in breast cancer tissues, which is linked to increased tumor aggressiveness and resistance to therapy. By regulating key oncogenes and affecting processes like proliferation, invasion, and apoptosis, miR-145 is crucial in cancer biology. Restoring miR-145 levels may improve treatment effectiveness and help overcome drug resistance. Additionally, its potential as a biomarker for diagnosis and prognosis enhances its clinical relevance. The study lays the groundwork for future research into miRNA-based therapies involving miR-145, aiming to transform breast cancer treatment and patient outcomes.

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