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Cancer Prognosis and miRNA

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Abstract

The micro ribonucleic acids are commonly referred to as MicroRNAs, miRNAs or µRNA. These micro-nucleic acids are very short and single-stranded RNA molecules composed of 19 to 25 nucleotides. miRNAs play an important regulatory role in the cells of many organisms including humans, animals, and plants. miRNAs were discovered in 1993 and the role and mechanism of action of these molecules is still under investigation. Recently, it has been confirmed that the non-coding miRNAs play an essential role in gene regulation. Considering the role of miRNAs in many biological and pathological reactions and mechanisms, especially cancer, scientific interest in these molecules is increasing as these molecules are believed to hold great promise as a therapeutic approach. The discovery of miRNAs is considered as the beginning of a new age in molecular biology. This article will provide an outlook on miRNAs, the stages of their biogenesis, types of miRNAs and their role in cancer initiation and progression. Therefore, the aim of this research is to identify the biological mechanisms by which miRNAs can influence cellular functions that are disrupted in the initiation and progression of cancer. In addition, this research also aims to demonstrate the potential of utilizing miRNAs in the diagnosis and therapy of different types of cancer.

Keywords microRNA, miRNA, µRNA, TSmiRNAs, OncomiRNAs, Cancer

1. Introduction

The micro ribonucleic acids (miRNAs) are single-stranded small non-protein-coding RNAs (ncRNAs) that are 19 to 25 nucleotides in length (Lu and Rothenberg, 2018; Fu et al., 2021). miRNAs make up about 3% of the human genome. 50% of miRNAs are located in “fragile sites” in the genome (Mishra et al., 2016). Although miRNAs do not encode proteins, they regulate gene expression post-transcriptionally (Lu and Rothenberg, 2018; Zhang et al., 2013) by binding to the 3' untranslated region (UTR) of mRNAs, leading to mRNA degradation or inhibition of translation and thus down-regulation of target proteins (Meier et al., 2013). While miRNAs generally interact with the 3' UTR of target mRNAs to reduce expression, they may also interact with other regions such as the 5' UTR, coding sequence and gene promoters, and may even activate gene expression under certain conditions. Recent research suggests that miRNAs are transported among the many different parts of cells to regulate translation and

transcription rates (Dinçer, 2023). Even a single miRNA is able to influence and alter the expression of a set of genes therefore miRNA has an important genetic regulatory role in a lot of physiological and pathological processes (Hartmann and Tacke, 2016). The majority of miRNAs are located in the intronic regions of protein-coding genes, but they may also be found in intergenic regions or exons (Kozomara et al., 2019). miRNAs were first recognized in 1993 while Lee and colleagues conducted their studies on Caenorhabditis elegans. At the time, miRNAs were not understood by them and were described as tiny non-coding RNAs organizing the development of Caenorhabditis elegans larvae. Lee and colleagues named the first member of the miRNA family as lin-4 (Lee et al., 1993). Essential functions of miRNAs became clear only after the detection of let-7 in D. melanogaster and humans. However, the first use of the term miRNA was introduced in 2001. In the following studies, it has been shown that miRNAs are also found in animals, plants and viruses. Additionally, miRNAs have also been identified with functions in regulating gene expression (Lukman Anwar et al., 2020). The association of miRNAs with cancer was first demonstrated by Calin and colleagues in the year 2002 when it was shown that defects in miRNA-15 and miRNA-16 cause deletion of chromosome 13q14 and thus play a role in the onset of chronic lymphocytic leukemia (CLL) (Calin et al., 2002). Since then, miRNAs have been found in all animal model systems. New miRNAs are still being discovered and their role in gene regulation is becoming increasingly well understood (Friedländer et al., 2014). In the following studies, great contributions have been made to the literature on the structure and function of miRNAs (Dinçer, 2023). According to the latest miRBase data, which catalogs, labels and distributes miRNA gene sequences, there are now 48,860 miRNAs in 271 organisms, including plants, animals and some microorganisms. In addition, the number of human mature miRNAs identified is more than 2654 (miRbase, 2024). The miRNA genes are localized all over the genome (Hammond, 2015). miRNAs are synthesized in a three-phase biological process of regulation (Lukman Anwar et al., 2020). The first stage is the transcription of primary miRNAs (pri-miRNA). The process of miRNA biosynthesis is initiated by post / co-transcriptional processing of RNA polymerase II/III transcripts (Winter et al., 2009). miRNAs are synthesized as primary transcripts (pri-miRNA) from genomic DNA by the enzyme RNA polymerase II (Bašová et al., 2017). Pri-miRNA has a “cap” and “poly A” tail and is converted in the nucleus by Drosha, an endonuclease of the RNAase III enzyme family, and its cofactor Pahsa (or DGCR8) into pre-miRNA of approximately 70 nucleotides in length (Elton et al., 2012). In the second stage, pri-miRNAs are converted into precursor miRNAs (pre-miRNAs) in the nucleus (Hammond, 2015). The resulting pre-miRNA molecule is transported into the cytoplasm in a manner dependent on the nuclear transport receptor Exportin 5 (a RanGTP-dependent dsRNA-binding protein) and the nuclear protein RAN-GTP (Catalanotto et al., 2016; Ali Syeda et al., 2020). In the third stage, mature miRNAs are formed in the cytoplasm. pre-miRNAs are cut by Dicer endonuclease belonging to the RNAase III enzyme family and converted into double-stranded miRNAs with 18-25 nucleotides in length (Karagün, 2014). In addition, Dicer initiates the formation of the RNA-induced silencing complex (RISC) (Catalanotto et al., 2016; Salehi et al., 2024). After the stem-loop of the pre-miRNA is cut by Dicer, only one of the miRNA duplexes joins the RISC complex. This strand is termed the guide strand. The other strand is termed the anti-guide (passenger strand) and is being digested as a substrate for the RISC complex (Elton et al., 2012). The miRNA sequences will be dispersed all over the genome and will be classified as intergenic or intronic miRNAs (Hussen et al., 2021). MiRNAs can bind to the 3'-untranslated region (3'UTR) of target mRNAs and affect gene expression, which results in mRNA fragmentation and/or translational inhibition, thus down-regulating the expression of target proteins (Zhang et al., 2013). The majority of mature miRNAs are present in the cytoplasm and bind to target mRNAs. Additionally, miRNAs occur in the extracellular space via the active exudation, passive release, or encapsulation in extracellular vesicles including exosomes. These exosomes

act as messengers for the intercellular transfer of miRNAs. Such miRNAs, known as Exosomal-miRNAs (ExomiRs), are secreted by cancer cells and can be taken up by neighboring cells. They thereby alter gene expression and cellular behavior (Salehi et al., 2024). Each miRNA regulates different biological processes by controlling hundreds of target genes (Elton et al., 2012; Rothschild, 2014). If miRNAs bind to the 3' UTR region of the mRNA, so-called imperfect complementarity occurs, leading to inhibition of translation. However, if the binding occurs inside the ORF region, so-called perfect complementarity occurs, in which case mRNA degradation by Ago2 occurs (Hayes et al., 2014). In order to gain a clearer picture of the influence of miRNA activities, a genome-wide analysis of their targets is necessary (Meier et al., 2013).

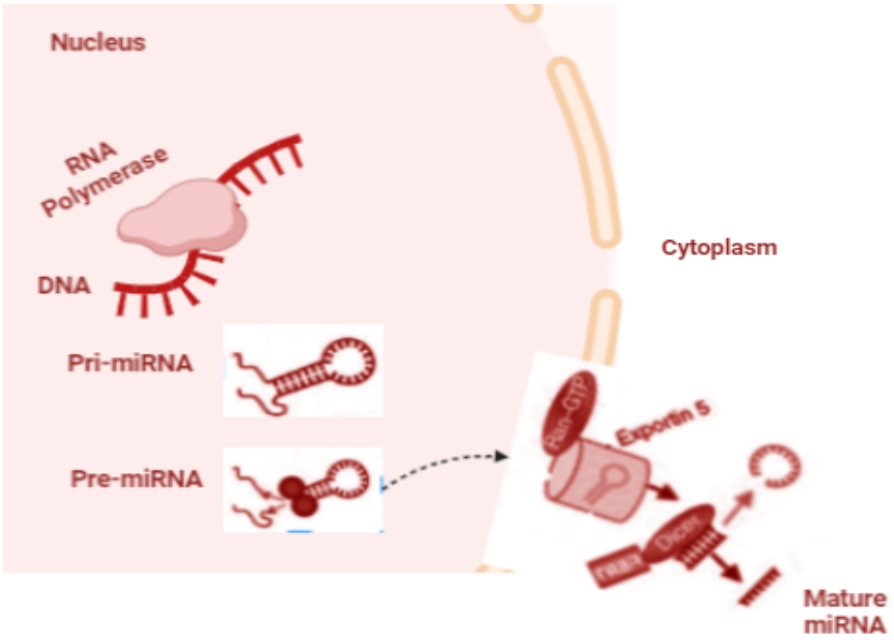

Figure 1. Stages of miRNA biogenesis

Due to increasing scientific evidence suggesting a relationship between miRNAs and cancer, the aim of our study is to determine the role that miRNAs play in stimulating or preventing the initiation and development of cancer. Most studies that focus on the relationship between miRNAs and cancer investigate whether or not miRNAs can be used as a biomarker for cancer. In our study, we aimed to demonstrate the mechanisms by which miRNAs cause cancer. For this purpose, we conducted a search for studies that relate to our study topic. We then identified the biological mechanisms that miRNAs can affect, leading to the development of cancer.

2. Methodology

This article was conducted to give a comprehensive overview of the relationship between miRNAs and cancer. We aimed to have a comprehensive review on this topic that enables the reader to get a complete but informative perspective on the topic of study. Initially, the following electronic databases were searched: PubMed, Web of Science, Scopus and Google Scholar. The following keywords were used during the database search: MicroRNAs, microRNAs and cancer, microRNAs and pathways, microRNAs and cancer therapy, types of microRNAs, microRNAs as biomarkers. Then, duplicate articles were excluded. Titles and abstracts were then manually screened and articles that did not meet the topic of the study were excluded. Thereafter, the articles were selected based on two criteria: I. most relevant II. most recent.

3. Types of miRNAs

Depending on their target genes, miRNAs function mainly as tumor Suppressor miRNAs (TSmiRNAs) or oncogenic miRNAs (OncomiRNAs) (Ali Syeda et al., 2020). They are consequently accepted to be noninvasive biomarkers in order to detect and diagnose cancers. Modulating the expression levels of both TSmiRNA and OncomiRNA can influence tumors due to their ability to induce changes in cancer cell behaviors (Grace et al., 2024). One miRNA can target more than 200 genes which makes it difficult to determine which target pathways are regulated by a particular miRNA. Studies have shown that some types of miRNAs can play a variable role in tumors. Some tumors can act as tumor suppressors while others can act as oncogenic activators (Otmani and Lewalle, 2021).

3.1 TSmiRNAs

miRNAs that have the function of controlling the expression of an oncogene are called tumor suppressor miRNAs (TSmiRNAs) regulation (Lukman Anwar et al., 2020; Hussen et al., 2021). TSmiRNA contributes to the inhibition of carcinogenesis (Otmani and Lewalle, 2021), therefore its under-expression leads to dysfunction in many cellular processes similar to apoptosis, cell growth, invasion and metastasis (Taniguchi et al., 2019; Grace et al., 2024). TSmiRNA not only affects cancer cells but also the tumor microenvironment (TME). The decreased TSmiRNAs expression affects cancer-associated fibroblasts in TME leading to increased proliferation and metastasis and increased tumor expansion. Missing some TSmiRs was linked to higher tumor aggressiveness and poor prognosis (Grace et al., 2024). The tumor-suppressing activities of several miRNAs have been revealed in a lot of studies. Tumor suppressor activities of miRNA-15a and miRNA16-1, which are reported to inhibit uncontrolled cell growth at normal levels (Calin et al., 2008). Another miRNA with tumor suppressor properties is a members of the let-7 family (let-7b, let-7c, let-7d, let-7f and let-7g). Studies found that let-7 expression levels were low in lung cancer tissues (Takamizawa et al., 2004; Kim et al., 2012) as let-7 controls the expression of RAS which is one of the oncogenes (Johnson, 2005). Low expression of miRNA-29 family genes has been shown to lead to chronic lymphocytic leukemia (Calin et al., 2005), invasive breast cancer (Iorio et al., 2005) and cholangiocarcinoma (Mott et al., 2007). Meanwhile many studies demonstrated that miRNA-143 inhibits abnormal cell growth (Amaral et al., 2009; Lin et al., 2009). In addition, both miRNA-34 (Hammond, 2015) and miRNA-200 contribute to the suppression of tumor development (Otmani and Lewalle, 2021). Furthermore, the expression of miRNA-96, miRNA-99a, miRNA-125b, miRNA-145, miRNA-203, miRNA-214, miRNA-411, and miRNA-486 is reduced in many tumors (Grace et al., 2024).

3.2 OncomiRNAs

OncomiRNA expression is increased during tumor formation as it inhibits the expression of anti-tumor genes and thus initiates tumor formation (Taniguchi et al., 2019; Otmani and Lewalle, 2021). Oncogenic miRNAs, which function differently from tumor suppressor miRNAs, often exhibit uncontrolled growth-promoting and/or antiapoptotic functions in cancer regulation (Lukman Anwar et al., 2020). miRNA-155 is one of the first oncogenic miRNAs discovered to be co-expressed with the protein-deficient BIC gene. In most studies, miRNA-155 has been found to be highly expressed in tumor diseases including B-cell lymphoma, lung, breast, pancreatic and Hodgkin lymphoma (Iorio et al., 2005; Hussen et al., 2021). A number of oncomiRNAs have been shown to express increased abundance and mediate cancer pathogenesis, including increased levels of miRNA-19a (Kim et al., 2012), miRNA-181b (Li et al., 2012) or miRNA-24 in tumor tissue (Wu et al., 2012). In addition, some studies showed that miRNA-20a, miRNA-19b-1, miRNA-92-, miRNA-17-92, miRNA-372, miRNA-373,

miRNA-9, miRNA-10b, miRNA-29a, miRNA-92a, miRNA-148a-3p, miRNA-222, and miRNA-373 expression levels increased in many cancers (Grace et al., 2024).

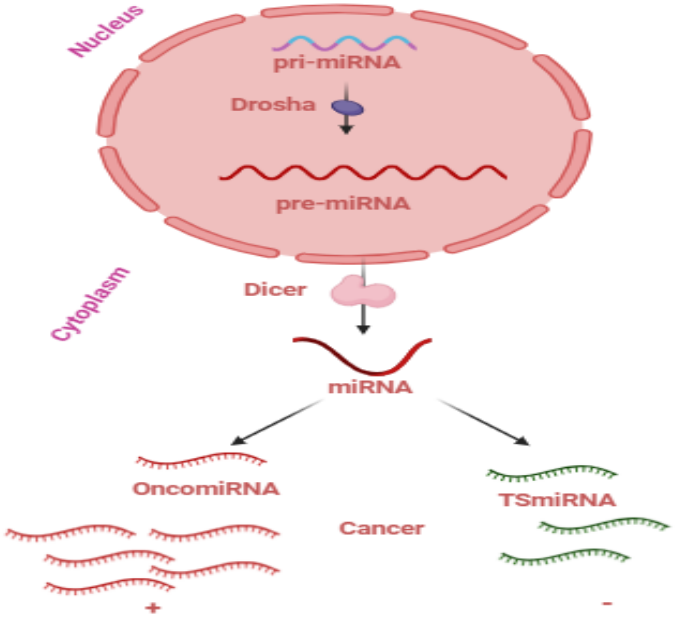

Figure 2. Action mechanism of OncomiRNAs and TSmiRNAs

4. miRNAs Functions

It can be noted that a major revolution in the field of genomics and molecular biology occurred after 2000 with the discovery of miRNAs (Li et al., 2021). Before this, cancer-causing genes were seen as the only cause of cancer. However, after the discovery of miRNAs, miRNAs have been reported to be dysregulated in many cancerous tissues, therefore, the number of researches looking to determine the relationship between miRNAs and cancer is increasing (Hammond, 2015). Although many of the biological functions of miRNAs are still unknown, it has been proven that any disruption in miRNA expression contributes significantly to the initiation and progression of cancer (Taniguchi et al., 2019; Hussen et al., 2021). As a consequence of the multiple targets of cancer-associated miRNAs (Mishra et al., 2016) their gene expression varies from one cancer type to another (Calin et al., 2002). The various studies that have focused on determining the functions of miRNAs have identified some of their functions;

-Up-to-date, studies revealed that approximately 60% of human protein-coding genes are regulated by miRNAs (Elton et al., 2012).

-Studies also revealed that miRNAs play a pivotal role in many cellular functions such as cell growth and development, differentiation, apoptosis, cell proliferation (Lima et al., 2017), lipid and glucose metabolism (Hartmann and Tacke, 2016) and cellular response to environmental stressors (Otmani and Lewalle, 2021).

-In addition, studies revealed that misregulated miRNA expression is associated with certain human diseases (MacFarlane and Murphy, 2010; Ali Syeda et al., 2020), such as heart disease (Cameron et al., 2008), neurodegenerative (Gonzalez-Alegre, 2007), and inflammation (hepatitis C) (McCaffrey et al., 2002).

-miRNAs play an important role in regulating the immune system as they contribute to stem cell maintenance (Mraz et al., 2012), 3, primary B cell formation, B cell development, intercellular interactions at immune niches and the production of immunoglobulins (Musilová and Mráz, 2015).

-miRNAs play a role in cancer initiation, cancer progression, invasion, metastasis (Karagün, 2014; Musilová and Mráz, 2015; Saffar et al., 2024) and resistance to treatment (Li et al., 2021).

-Since miRNAs are stable in blood, saliva, and cell lines, they play a role as non-invasive biomarkers. miRNAs can be used in identifying tumors, stratifying patients, and predicting tumor responses to treatment (Lukman Anwar et al., 2020).

5. miRNAs and Cancer

Despite advances in the diagnosis and treatment of cancer, it continues to represent one of the most important health issues worldwide. Therefore, scientists are still investigating the factors involved in the initiation and development of cancer. miRNAs are involved in regulating the expression of many genes. Disturbances in the expression of miRNAs either by decreasing or increasing can lead to the development of many diseases, including cancer (Smolarz et al., 2022).

5.1 miRNAs, cell cycle and cell proliferation

The cell cycle involves four phases, which are Gap 0/1 (G0/G1), Synthesis (S), Gap 2 (G2), and Mitosis (M). These phases are regulated by cyclin dependent kinases (CDKs). Before and during cancer formation, the cell cycle is disrupted (Garrido-Cano et al., 2022). Studies have shown that miRNAs play a role in targeting genes that control the cell cycle and thus play a pivotal role in cancer formation. miRNA-34b-3p targets CDK4 kinase which is important for cell cycle progression in G1 phase so inhibition of its expression leads to cell cycle progression (Feng et al., 2019). miRNA-543 inhibits the ERK/MAPK pathway which plays a role in cell cycle progression and thus prevents cell division (Chen et al., 2017). miRNA-7 targets cyclin E1 (CCNE1) which regulates the G1/S transition and thus affects the cell cycle. Yang et al. showed that both miRNA-30b and miRNA-26a target cyclin E2 (CCNE2) and lead to cell cycle arrest in G1 (Yang et al., 2019). miRNA-34a targets cyclin D1, which leads to cell cycle arrest. miRNA-26a targets CDK6, which regulates the cell cycle transition from G1 to S, thus leading to cell cycle arrest (Dinçer, 2023). miRNA-93 also plays a role in cell cycle arrest in the G1/S phase (Bao et al., 2020). miRNA-9 targets both cyclin-dependent kinase 6 (CDK6) and cyclin D1 which induces cell cycle arrest (He et al., 2020). Conversely miRNA-26a-5p inhibits p27 expression which leads to increased cell proliferation (Dinçer, 2023). On the other hand, miRNA-519a, miRNA-22-3p, and miRNA-663b were found to target the PI3K/AKT pathway which is an important pathway in the cell cycle (Ward et al., 2014). miRNA-663b also regulates the expression of TP73 which inhibits the cell cycle (Garrido-Cano et al., 2022). In addition, miRNA-1269 targets both the AKT and Bax/Bcl-2 pathways, accelerating the G1-S cell cycle transition (He et al., 2020). In the same way, miRNA-21 targets PTEN, which leads to enhanced activation of the PI3K/AKT pathway and cell cycle acceleration (Dinçer, 2023). The Wnt/b-catenin pathway stimulates cancer cell proliferation leading to tumor initiation and progression. Therefore, TSmiRNAs inhibit tumor cell proliferation by suppressing Wnt/b-catenin pathways (Otmani and Lewalle, 2021). Higher levels of miRNA-340, which operates like a TSmiRNA, inhibit Wnt expression and suppress cell proliferation (Otmani and Lewalle, 2021). However, both miRNA-145, miRNA-487a, miRNA-133a-5p (Taniguchi et al., 2019). miRNA-34a (Otmani and Lewalle, 2021), miRNA-145 (He et al., 2020). miRNA-19 plays a key function in regulating the cell cycle and thus cell division and proliferation (Otmani and Lewalle, 2021).

5.2 miRNAs and growth receptors

Overexpression, amplification or mutations in genes responsible for growth receptors lead to dysregulation of these receptors. Overexpression of growth receptors is associated with enlarged tumor size and poor clinical outcomes by promoting the malignant phenotype of cancer (Garrido-Cano et al., 2022). miRNAs have been shown to regulate cancer cell

proliferation by targeting genes involved in growth factor signaling pathways, thus enhancing or inhibiting their functions (Gomez et al., 2013). miRNA-205 targets HER3 which is a growth factor receptor that activates the PI3K/AKT pathway leading to reduced cell proliferation (Stankevicins et al., 2017). miRNA-22 acts by reducing or losing PTEN expression and this leads to the acceleration of Akt pathway activity and thus stimulates growth factors in cancer cells. miRNA-223 acts to reduce cell growth by inhibiting the insulin-like growth factor 1 receptor (IGF1-R) (Jia et al., 2011). miRNA-375 targets IGF1R. IGF1R contributes to increased growth of cancer cells so low miRNA-375 expression increases the growth of cancer cells (Garrido-Cano et al., 2022). miRNA-26a/b suppresses HER2 translation (Tan et al., 2017). miRNA-137 inhibits the EGFR/PI3K pathway by targeting EGFR (Ma et al., 2019). miRNA-630, miRNA-200c and miRNA-199b-5p suppresse tumors overexpressing HER2. Because their overexpression leads to a decrease in the levels of IGF1R, EGFR, and HER2 receptors. miRNA-205, miRNA-125a, and miRNA-205 suppress tumors by suppressing the expression of HER3. On the other hand, studies have shown that miRNA-10b and miRNA-575 promote estrogen receptors (ER) while miRNA-221, miRNA-222 and miRNA-335 suppress ER receptors (Corcoran et al., 2014).

5.3 miRNAs, tumor microenvironment and neo-angiogenesis

Some miRNAs have the ability to influence the tumor microenvironment by regulating the function of immune cells (Elnaggar et al., 2021). Some miRNAs also regulate intercellular communication through their effect on stromal cells and extracellular matrix components. Therefore, miRNAs dysregulation leads to the microenvironment becoming a suitable medium for tumor growth and cancer cells bypassing the immune response (Hussen et al., 2021). miRNA-155 carries out a mission in the neoangiogenesis of tumor cells by targeting the VHL gene. miRNA-155, miRNA-19a, miRNA-181b, and miRNA-24 also contribute to the formation of new blood vessels in tumor cells by targeting transforming growth factor (TGF) (Bašová et al., 2017). Both miRNA-210 and miRNA-519c control the angiogenesis of cancer cells upon hypoxia by modulating hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF) (He et al., 2020). On the contrary, miRNA-200c increases the immune response in cancer environment thereby reducing angiogenesis (Hussen et al., 2021). miRNA-29 inhibits B7-H3 gene expression. This leads to an increase in angiogenesis in the area surrounding the tumors.

5.4 miRNAs and metastasis

Epithelial-mesenchymal transition (EMT) is when epithelial cells lose their adhesion to neighboring cells and acquire new properties that allow them to migrate, invade, and metastasize (Dinçer, 2023). Many miRNAs target genes that regulate EMT process (Otmani and Lewalle, 2021). This process is caused by the loss of expression of epithelium-associated genes such as CDH1. This process can also be caused by an increase in the expression of mesenchyme-associated genes such as N-cadherin (CDH2), vimentin (VIM), and fibronectin (FN1). In this process, cells acquire new properties that enable them to invade, migrate and settle in new tissues and thus metastasis occurs. miRNA-200 family members target ZEB1 and ZEB2, transcription factors that promote EMT and metastasis. Rothe´and colleagues showed that increased miRNA-210 expression leads to invasion and metastasis of cancer miRNA-155 targets RhoA which plays an important role in EMT (Chen et al., 2012). In addition, studies have shown that miRNA-519a, miRNA-223, miRNA-205 (Li et al., 2021), miRNA-19a, miRNA-181b (Bašová et al., 2017), miRNA-126, miRNA-129-5p, miRNA-106b, and miRNA-93 (Garrido-Cano et al., 2022) activate the EMT process. On the contrary, other studies have shown that miRNA-34a (Li et al., 2012), miRNA-340 (Chen et al., 2012), miRNA-708-3p,

miRNA-125 and miRNA-137 inhibit the EMT process and thus metastasis does not occur (Garrido-Cano et al., 2022).

5.5 miRNAs and apoptosis

Cell death process is one of the most important cellular processes. Cell death occurs in the form of apoptosis, autophagy, or programmed necrosis. Many studies have demonstrated that miRNAs play an important role in regulating cell death because they target many genes involved in cell death pathways (Breunig et al., 2017). Calin and colleagues (2002) reported that the gene region encoding miRNA-15a and miRNA-16-1 is frequently deleted or translocated in B-cell CLL patients. As a result of the deletion, the expression level of the antiapoptotic BCL-2 (B-cell lymphoma 2) protein, which is the target of miRNAs, increases and the cells do not go to apoptosis (Calin et al., 2002). miRNA-519a-3p mediates apoptosis resistance in breast cancer cells and their evasion from recognition by natural killer cells by targeting caspase-8 and MICA proteins. miRNA-21 can inhibit the proliferation of cancer cells and even cause programmed cell death (apoptosis) (Breunig et al., 2017). In addition, studies proved that miRNA-134, miRNA-31 (Hayes et al., 2014), miRNA-489, miRNA-34a (Garrido-Cano et al., 2022) and miRNA-148a (Elnaggar et al., 2021) play a role in the process of cell death through the translational repression of BCL-2. miRNA-1307 also contributes to the inhibition of p53, highlighting its importance in the process of cell death. miRNA-424 and miRNA-21-5p participate in apoptosis by targeting PDCD4 (Garrido-Cano et al., 2022).

6. Cancer Therapy Utilizing miRNAs

Many studies demonstrated that miRNAs take on a critical role in the regulation of cancer due to their ability to influence many cellular processes. For this reason, many researchers believe that studies on cancer therapy must focus on miRNAs as therapeutic targets for cancer (Taniguchi et al., 2019). On the other hand, unlike some biomarkers used in cancer diagnosis that do not differentiate between benign and malignant tumors, the expression of miRNAs that are clearly different between normal and cancerous cells may be the key to diagnosing cancers (Dharanija et al., 2013). The researchers identified rearrangements in regions of genes containing miRNAs and experiments showed that their expression levels are significantly altered in cancer cells (Hussen et al., 2021). miRNA-related cancer therapies are considered to be either miRNA mimetics that restore or compensate for the under-expression of miRNAs, or inhibitors of OncomiRNAs that are overexpressed in cancer (Zhang et al., 2013). The benefit of modifying the expression of miRNAs in place of genes is that they can target several different genes and pathways at the same time. Moreover, the implementation of miRNA-related therapy will play a role in minimizing the resistance risk to other treatments used in cancer (Hussen et al., 2021). In summary, although miRNA-related cancer therapies are still new and experimental, they have provided promising results. More research needs to be done in this area to reach the ultimate aim of optimizing patients' overall survival (He et al., 2020).

7. Conclusion

Studies in recent years have shown that miRNAs are critical in gene regulation and cell carcinogenesis. This is because miRNAs play an important role in regulating a large number of cellular processes. Therefore, any disruption in the gene expression of miRNAs will lead to the development of cancer. However, studies to date have failed to provide a precise and detailed understanding of the self-regulation of miRNAs. The fact that miRNAs are stable molecules in body tissues and fluids makes them potential diagnostic tools for cancer detection, but more research is still needed in this field. Indeed, owing to the growing understanding of cellular biology and the recent technological progress, miRNAs are increasingly becoming attractive tools and targets for new therapeutic and molecular approaches. The constantly growing understanding of miRNAs' function in cancer biology may well provide future directions for

the development of new therapies. The essential mechanism of the existing miRNA-based therapeutic research is to efficiently oppose the functionality of tumor-causing miRNAs or enhance the expression of tumor-suppressing miRNAs.

Limitations of the Review

An important limitation of our study is the language limitation as studies not published in English were excluded.

Strengths of the Review

A comprehensive literature search was conducted using a specific search strategy and multiple databases. In addition, our study includes comprehensive research and gives detailed information on the relationship between microRNAs and cancer.

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Ethics Permissions

This paper does not require ethics committee approval.

Author Contributions

Faten ALNOAIMI and Mehmet Özaslan contributed to the identification of the research objective. Faten ALNOAIMI drafted the manuscript. Mehmet Özaslan performed the proofreading, editing, and verification.

Conflict of Interest

Authors declare that there is no conflict of interest for this paper.

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