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Review

A thorough and current study of miR-214-related targets in cancer

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ABSTRACT

Cancer is a complex genetic anomaly involving coding and non-coding transcript structural and expressive irregularities. A class of tiny non-coding RNAs known as microRNAs (miRNAs) regulates gene expression at the post-transcriptional level by binding only to messenger RNAs (mRNAs). Due to their capacity to target numerous genes, miRNAs have the potential to play a significant role in the development of tumors by controlling several biological processes, including angiogenesis, drug resistance, metastasis, apoptosis, proliferation, and drug resistance. According to several recent studies, miRNA-214 has been linked to the emergence and spread of tumors. The human genome's q24.3 arm contains the DNM3 gene, which is about 6 kb away and includes the microRNA-214. Its primary purpose was the induction of apoptosis in cancerous cells. The multifaceted and complex functions of miR-214 as a modulator in neoplastic conditions have been outlined in the current review.

1. Introduction

Cancer is a multifaceted genetic anomaly encompassing structural and expression irregularities of coding and non-coding transcripts. In 2002, a significant correlation between miRNAs and cancer was discovered when recurrent deletions were detected in a miRNA-coding region among 50% of patients diagnosed with B-cell chronic lymphocytic leukemia [7]. Subsequently, it has been demonstrated in the scientific realm that the dysregulation of miRNAs plays a significant role in the onset and advancement of cancer [12]. Furthermore, several miRNAs have been identified to possess either tumor-suppressive or oncogenic functions [23,47]. It has become evident that the neoplastic cells contain more genomic complexity than previously anticipated. Following these noteworthy discoveries, identifying and replicating diminutive, non-coding RNAs (ncRNAs) measuring approximately 22 nucleotides in length has acknowledged over 1000 miRNAs. MicroRNAs (miRNAs) are known to have significant involvement in a range of physiological and pathological processes. These include embryonic stem cell development, cell proliferation, apoptosis, differentiation, morphogenesis, multi-organ malformations, angiogenesis, vascular pathologies, immune response, autoimmune diseases, viral infection, and carcinogenesis [36]. MicroRNAs (miRNAs) are a class of small non-coding RNAs that exert their function through binding to the 3' untranslated region of their target messenger RNAs (mRNAs) in a sequence-specific manner. This interaction leads to the degradation or translational inhibition of the targeted mRNAs. The involvement of miRNAs in advancing various cancers is widely recognized [37]. The human miR-214, situated in the chromosomal region 1q24.3, is crucial in regulating tumor proliferation, angiogenesis, invasiveness, metastasis, and resistance to chemotherapy which has been documented in

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various studies [40].

This review aims to provide a broad overview of the literature surrounding the roles of miR-214 in cancer, first by outlining miRNA biogenesis. Tumor proliferation, drug resistance, apoptosis, metastasis, stemness, and angiogenesis are then discussed in the context of miR-214. Understanding these roles helps realize the potential of modulating miR-214 for therapeutic benefit.

2. miRNA biogenesis

Two decades ago, the established tenet in molecular biology was the classical dogma that DNA undergoes transcription to produce RNA, which is then translated into proteins. The advent of whole-genome and transcriptome sequencing technologies has revealed that over 90% of the genome is transcriptionally active. Remarkably, a mere 2% of the genome encodes proteins, whereas the remaining transcriptome exhibits a significant expression of non-coding RNA (ncRNA) [13]. Formerly, these molecules were deemed insignificant; however, a substantial proportion has been discovered to participate in most cellular processes and functions [5]. Currently, microRNAs (miRNAs) are a well-documented class of small non-coding RNAs that are the focus of extensive translational research. 1993 Ambros et al. [26] and Ruvkun et al. [60] identified lin-4 as the inaugural miRNA in Caenorhabditis elegans. Its crucial role in regulating developmental timing was established.

The December edition of the Cell journal featured reports by Ambros and Ruvkun, highlighting the regulatory role of the small and non-protein-coding transcript lin-4 on mRNA lin-14 *via* its 3' UTR region. The reduction in LIN-14 protein expression was contingent upon the transcriptional activity of lin-4, a non-coding RNA molecule that does not undergo translation into a protein [60]. The second miRNA was identified only in the year 2000, as reported by Ruvkun et al. [43]. Let-7, a heterochronic gene found in C. elegans, regulates the transition of larval development by binding to two closely spaced sites in the lin-41 3'-untranslated region (3'-UTR). Significantly, the let-7 sequence exhibits high conservation among various species ranging from Drosophila melanogaster to Homo sapiens [38]. The let-7 family in humans comprises 12 miRNAs with identical sequences in the seed region, thereby governing similar targets [50]. The information mentioned above held considerable importance in examining miRNAs in diverse organisms. Subsequently, many miRNAs have been discovered in various organisms, including humans. As per the present iteration of the miRBase repository, annotations have been made for 38,589 hairpin precursors and 48,860 mature miRNAs derived from 271 distinct organisms. The human genome comprises 1917 hairpin precursors and 2654 mature sequences [25].

miRNAs are a class of small non-coding RNAs that are highly conserved across species. They regulate gene expression by binding to the 3'-UTR of target mRNA, with the binding being imperfect. In general, miRNA binding to the target transcript *via* partial complementarity results in either degradation of the transcript or repression of its translation [1]. The biogenesis of miRNAs is characterized by a specific process that enables their expression to be regulated spatially and temporally [15]. The transcription of miRNA genes results in the formation of primary transcripts (pri-miRNA) that contain hairpins. The process of generating short hairpin pre-miRNAs from pri-miRNAs occurs in the nucleus through the cleavage of the former by the Double-Stranded RNA-Specific Endoribonuclease DROSHA (RNase III) and it's cofactor DiGeorge syndrome Critical Region 8 (DGCR8). The Exportin-5 RanGTP complex facilitates the transportation of pre-miRNAs from the nucleus to the cytoplasm, where they undergo additional processing by the Dicer RNase III/TRBP complex to form mature miRNAs consisting of approximately 22 nucleotides in a double-stranded configuration. Subsequently, the small RNA duplex that ensues is incorporated into the RNA-Induced Silencing Complex (RISC) employing the AGO (Argonaute) protein. The guide strand is specifically chosen within the RISC to execute its impact on the target transcript, as indicated by previous research [27].

3. miRNA-214 genomic biology

The microRNA-214 is located in the dynamin 3 (DNM3) gene in the q24.3 arm of the human genome. A distance of around 6 kilobases separated it, and it was first identified for its ability to induce apoptosis in HeLa cells [10]. Subsequently, it has been associated with various health conditions such as cardiovascular disorders, malignancies, skeletal growth, and cellular differentiation [40,73]. MiR-214 has been observed to safeguard the heart from Ca2 + ion overload and oxidative damage. However, it has been found to suppress angiogenesis and potentially encourage pathological fibrosis [3,4,34], though this is unclear [76]. It is worth noting that some researchers have challenged this assertion. A growing body of evidence suggests that dysregulation of miR-214 may be a contributing factor in the development of various types of human tumors, such as hepatoblastoma, hepatocellular carcinoma, gastric cancer, esophageal squamous cell carcinoma, lung cancer, breast cancer, osteosarcoma, pancreatic cancer, cervical cancer, prostate cancer, ovarian cancer, bladder cancer, and melanoma. The reciprocal actions of miR-214 in diverse tumor tissues offer valuable insights into its multifaceted role in tumorigenesis and tumor suppression across multiple cancer types [14,65]. According to certain researchers, miR-214 is considered a tumor suppressor. Promoting epithelial-mesenchymal transition (EMT) in intrahepatic cholangiocarcinoma was facilitated by directly targeting the Twist gene through downregulating miR-214, as evidenced by previous research [28]. The study conducted by Shih et al. revealed that a reduction in miR-214 expression in individuals with hepatocellular carcinoma (HCC) was linked to a poorer prognosis. It developed de novo hypervascular HCC by stimulating hepatoma-derived growth factor secretion [48].

Conversely, miR-214 has been considered an oncogene in several other types of tumors. The overexpression of miR-214 in breast cancer tissues was found to significantly promote the invasion of tumor cells by inhibiting the expression of p53, as reported in a previous study [54]. Similarly, miR-214 exhibited overexpression in gastric cancer (GC). Notably, suppressing miR-214 in GC cells significantly reduced The variance in miR-214-mediated aggressive behavior could be attributed to the regulation of distinct genes by miR-214, which activate disparate predominant pathways across diverse cancer types. The regulatory role of miR-214 has been evidenced in various biological processes, including but not limited to proliferation, drug sensitivity, metastasis, apoptosis, stemness, and angiogenesis (Fig. 1) [8,31,66].

4. miRNA-214 and cancer characteristics

4.1. Proliferation

The targeted modulation of miR-214 resulted in a notable decrease in the rate of cell proliferation in breast cancer cells, as well as a significant inhibition of the invasive capacity of a breast cancer cell line that exhibited a high degree of metastatic potential. The results suggest that the decrease in miR-214 levels could be a factor in the development of breast tumors by facilitating the abnormal buildup of Ezh2 and uncontrolled cell growth; this aligns with previous research [11]. The study conducted by Yang and colleagues provided evidence that miR-214 targets Wnt3a as a gene of interest. Furthermore, it has been suggested that miR-214 can potentially impede the proliferation of liver cancer cells by targeting Wnt3a. The data above furnish empirical support for the proposition that miR-214 suppresses tumors by inhibiting the Wnt/β-catenin signaling pathway [67]. The findings indicate that the expression of miR-214 was notably reduced in both the tissue specimens obtained from individuals with colorectal cancer (CRC) and the cell lines derived from CRC. The overexpression of TFAM was also detected in patients with CRC and was recognized as a subject of interest

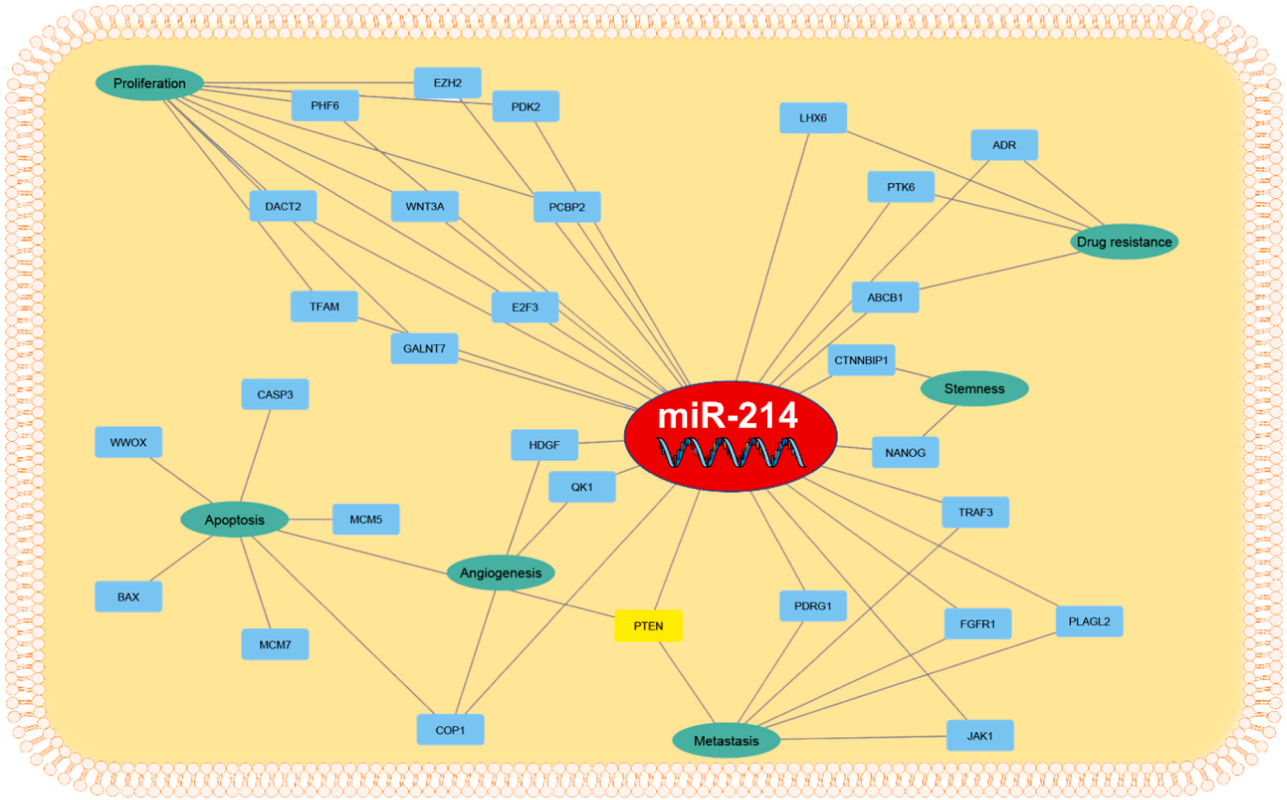

Fig. 1. The schematic overview of the targeting ability of miR-214 and its consequences in cancer progression. miR-214 affects proliferation, stemness, drug resistance, angiogenesis, apoptosis, and metastasis in cancer by targeting diverse target genes. PHF6: plant homeodomain (PHD)-like finger protein 6; EZH2: Enhancer of zeste homolog 2; PDK2: Pyruvate dehydrogenase kinase 2; PCBP2: Poly(rC) binding protein 2; WNT3A: Wingless/Integrated 3A; E2F3: E2F Transcription Factor 3; TFAM: Mitochondrial transcription factor A; GALNT7: polypeptide-N-acetyl-galactosam inly transferase 7; WWOX: WW domain containing oxidoreductase; CASP3: Caspase-3; BAX: Bcl-2-associated X protein; MCM: Minichromosome maintenance complex component; QK: Quaking homolog; PTEN; Phosphatase and TENsin homolog deleted; PDRG1: P53 And DNA Damage Regulated 1; LHX6: LIM Homeobox 6; PTK6: Protein tyrosine kinase 6; ADR: Adverse drug reaction; ABCB1: Adenosine 5′-triphosphate–binding cassette subfamily B member 1; CTNNBIP1: Catenin beta interacting protein 1; NANOG: Nanog Homeobox; TRAF3: Tumor Necrosis Factor Receptor-associated Factor 3; FGFR1: Fibroblast growth factor receptor 1; JAK1: Janus kinase 1; PLAGL2: Pleomorphic adenoma gene like-2.

for miR-214. The proliferation of CRC cell lines was significantly inhibited by the knockdown of TFAM through miR-214 mimicry, as reported in a previous study [61]. The expression of miR-214 in cervical cancer is comparatively lower than in normal cervical tissues.

Furthermore, the overexpression miR-214 has been observed to impede proliferation and invasion. The present study has identified GALNT7 as a novel target gene of miR-214, which has been observed to be overexpressed in cervical cancer tissue samples. The results suggest that the suppression of miR-214 in cervical cancer could potentially facilitate the development of a malignant phenotype through the upregulation of GALNT7 [39]. Furthermore, miRNA-214 has been observed to interact with the 3'-untranslated region of poly(rC) binding protein 2 (PCBP2) mRNA, resulting in the degradation of the mRNA and subsequent reduction in protein expression. The study's findings indicate that the excessive expression of miR-214 imitates a notable inhibition.

In contrast, applying its antisense oligos increases the proliferation and growth of glioma cells. The reversal of the tumor-suppressive impacts of miR-214 on cell proliferation and growth was observed to be significant upon the restoration of PCBP2 [51]. The study revealed that miR-214 exerts a tumor-suppressive effect in HCC cells by directly targeting the E2F transcription factor 3 (E2F3), inhibiting tumor proliferation. The proliferation of SMMC-7721 cells (a type of HCC) was inhibited by either the enhanced expression of miR-214 or the silencing of E2F3 [66]. Furthermore, Yu and colleagues discovered that inhibiting cellular proliferation and migration *via* PDK2 or PHF6 depletion exhibited partial restoration upon down-regulation of miR-214.

Furthermore, the authors exhibited a reduction in the expression of the mesenchymal cell marker α-SMA and an elevation in the expression of the epithelial marker E-cadherin after the overexpression of miR-214, knockdown of pyruvate dehydrogenase kinase 2 (PDK2) or knockdown of plant homeodomain finger 6 (PHF6), respectively. These findings also indicated the inhibition of cell proliferation and migration [68]. miR-214 was found to downregulate the expression of the Dishevelled-associated antagonist of β-catenin (Dact2) gene and stimulate the Wnt/β-catenin signaling pathway, thereby promoting the expansion of gastric cancer (GC) [71].

4.2. *Drug resistance*

Over the past few decades, there has been significant advancement in chemotherapy drugs. However, the development of drug resistance in tumors has been a major contributing factor to treatment failure. The deviant expression of specific miRNAs may result in drug resistance by influencing the expression levels of genes that participate in stress responses, drug transportation, metabolism, cell survival, and cell demise [2]. The upregulation of Adenosine triphosphate binding cassette subfamily B member 1 (ABCB1) mRNA and P-glycoprotein (PGP) expression was observed in bone marrow mononuclear cells of chronic myeloid leukemia (CML) patients who exhibited resistance to imatinib mesylate (IM). The expression of ABCB1 and PGP was comparatively higher in K562R cells than K562 cells, which could be attributed to their distinct sensitivity towards IM. The present study observed a reduction in the expression miR-214 in bone marrow mononuclear cells obtained from patients exhibiting IM resistance and in K562R cells. Notably, miR-214 exhibited the capability to interact with the seed region of ABCB1 mRNA's 3'-untranslated region, thereby modulating its expression.

Furthermore, the overexpression of miR-214 reinstated sensitivity to IM in K562R cells, plausibly by modulating the expression of ABCB1. The findings suggest that the overexpression of ABCB1 mRNA and PGP in bone marrow mononuclear cells of chronic myeloid leukemia patients who exhibit resistance to imatinib mesylate treatment may be linked to the reduced expression of miR-214. Furthermore, it has been suggested that miR-214 could be involved in the development of imatinib mesylate (IM) resistance in patients with chronic myeloid leukemia (CML) through the regulation of ABCB1 expression [24]. In a study conducted by Semaan et al., it was shown that HCC treatment with oxaliplatin and sorafenib anti-cancer drugs was significantly improved through the use of engineered human cerebral endothelial cell-derived exosomes that carried elevated levels of miR-214 [46]. Additionally, it has been demonstrated that miR-214 performs a crucial function in developing resistance to erlotinib in non-small-cell lung cancer (NSCLC) cells and NSCLC patients possessing EGFR mutation. Suppression of miR-214 could potentially counteract erlotinib resistance in NSCLC by regulating the expression of its direct target gene, LIM Homeobox 6 (LHX6) [32]. The expression of miRNA-214 was elevated in PC-9GR cells resistant to gefitinib and the exosomes derived from these cells. The reversal of gefitinib resistance induced by exosomes derived from PC-9GR cells was observed *in-vitro* upon inhibition of exosomal miR-214 through antagomir. The efficacy of exosomes enriched with miR-214 antagomir in reversing gefitinib resistance was validated through *in-vivo* experimentation. The findings indicate that miR-214-mediated transfer of exosomes from gefitinib-resistant PC-9GR cells to sensitive PC-9 cells can confer resistance, as demonstrated for the first time in this study [70]. Furthermore, a notable upregulation of miR-214 expression was observed in tissues of esophageal squamous cell carcinoma. There was an inverse correlation observed between the expression levels of miR-214 and overall survival. A potential correlation exists between elevated levels of miR-214 and reduced efficacy of chemotherapy. The sensitivity of esophageal cancer cells to both P-glycoprotein-related and P-glycoprotein-nonrelated drugs could potentially be enhanced through the downregulation of miR-214. This downregulation may also lead to an increase in the accumulation of adriamycin (ADR) and a decrease in the amount of ADR released. The potential significance of miR-214 in the development of esophageal cancer has been suggested in previous research [74]. The examination of miRNA profiling in small and non-small cell lung cancers (SCLC/NSCLC) has demonstrated that miRNAs have the potential to impact radiotherapy responsiveness. The functional role of miRNA-214 in altering the radiotherapy response of NSCLC cells was demonstrated by Salim et al. by manipulating miRNA-214 expression. The induction of senescence mechanisms was observed in NSCLC cells upon downregulation of miRNA-214, resulting in increased sensitivity to ionizing radiation. The findings indicate that the upregulation of miRNA-214 demonstrated a consistent protective effect on radiosensitive NSCLC cells in response to ionizing radiation-induced cell death. The authors additionally ascertained that in conjunction with compromised apoptotic signaling induced by radiotherapy, the overexpression of miRNA-214 resulted in heightened phosphorylation of p38 mitogen-activated protein kinases (p38MAPK) and Forkhead Homeobox04 (FoxO4). The findings suggest that p38MAPK-α plays a protective role In ionizing radiation-induced apoptotic signaling. Overexpression of miRNA-214 led to resensitization of NSCLC cells to ionizing radiation upon inhibition of p38MAPK-α [44]. Cagle and colleagues have demonstrated that miRNA-214 targets PTK6, thereby inhibiting the tumorigenic potential and enhancing drug sensitivity of prostate cancer cells. According to their findings, miR-214 exhibits tumor suppressive properties in prostate cancer and has the potential to serve as a therapeutic target and biomarker [6]..

4.3. Metastasis

In a study by Chen et al., miR-214 was discovered to function as a novel regulator of liver metastasis in colorectal cancer (CRC). The down-regulation of miR-214 resulted in the up-regulation of its target, FGFR1, ultimately leading to the metastasis of CRC [8]. Furthermore, a recent investigation examined the expression of miR-214 and FGFR-1 in 65 instances of HCC and corresponding non-neoplastic tissue samples. The findings suggest the downregulation of miR-214 and overexpression of FGFR-1 in HCC compared to the corresponding non-neoplastic tissues. A correlation was observed between reduced expression of miR-214 and both portal vein invasion and early recurrence among patients diagnosed with HCC. Additionally, a significant correlation was observed between decreased expression of miR-214 and an increased positive rate of FGFR-1 in cases of HCC. The study's results indicated that the overexpression of miR-214 led to the downregulation of fibroblast growth factor receptor 1 (FGFR-1) expression and the inhibition of liver cancer cell invasion, as previously reported [56]. Zhou and colleagues have demonstrated a significant downregulation of miR-214–3p in CRC.

Furthermore, a robust association was discovered between the level of miR-214–3p and both the size of the tumor and the occurrence of lymphatic metastasis. The findings of this investigation have demonstrated that a diminished level of miR-214–3p expression and an elevated expression of downstream Pleomorphic adenoma gene 2 (PLAGL2) in colorectal cancer indicates an unfavorable prognosis. The study revealed that the PLAGL2/ Myosin heavy chain 9 (MYH9) axis was regulated by miR-214–3p, suppressing malignant behaviors in CRC [75]. The downregulation of miR-214, which may be attributed to the upregulation of SRF, has been found to promote the growth and metastasis of colorectal cancer through the activation of the Protein tyrosine kinase 6 (PTK6)/ Janus Kinase 2 (JAK2)/ Signal transducer and activator of transcription 3 (STAT3) pathway, as per previous research [30]. Huang et al. conducted a study on esophageal squamous cell carcinoma (ESCC) and found that the expression of miR-214 was notably reduced in ESCC tissues compared to normal tissues. They also observed a correlation between the down-regulation miR-214 and the up-regulated EZH2 protein expression, poor pathological grade, advanced tumor stage, and lymph node metastasis in ESCC. This study provides valuable insights into the pathogenesis of ESCC [21].

A recent investigation has indicated that diminished levels of miR-214 are a distinguishing characteristic of lung carcinoma, particularly in advanced-stage and metastasis cases. The findings of the *in-vitro* studies conducted on H1299 cells indicated a positive correlation between decreased levels of miR-214 expression and increased

Table 1
The role of miRNA-214 in different cancers.

Type of cancer	Target	Expression	Reference
Breast cancer	Ezh2	Downregulated	[11]
Liver cancer	Wnt3a	Downregulated	[67]
Colorectal cancer	TFAM	Downregulated	[61]
Cervical cancer	GALNT7	Downregulated	[39]
Glioma	PCBP2	Downregulated	[51]
Hepatocellular carcinoma	PDK2 and PHF6	Downregulated	[68]
Gastric cancer	Dact2	Up-regulated	[71]
Chronic myeloid leukemia	ABCB1	Downregulated	[24]
Hepatocellular carcinoma	P-gp and SF3B3	Downregulated	[46]
NSCLC	LHX6	Up-regulated	[32]
NSCLC	FoxO4	Up-regulated	[44]
Prostate cancer	PTK6	Downregulated	[6]
Hepatocellular carcinoma	FGFR-1	Downregulated	[56]
Colorectal cancer	PLAGL2-MYH9	Downregulated	[75]
Colorectal cancer	PTK6	Downregulated	[30]
Esophageal squamous cell carcinoma	EZH2	Downregulated	[21]
Lung cancer	Carboxypeptidase-D	Downregulated	[72]
Lung cancer	JAK1	Downregulated	[9]
Bladder Cancer	PDRG1	Downregulated	[59]
Gastric cancer	PTEN	Up-regulated	[62]
Lung cancer	Sufu	Up-regulated	[33]
Lung cancer	CTNNBIP1	Up-regulated	[41]
Ovarian cancer	p53/Nanog	Up-regulated	[64]

proliferation and migratory capabilities. The overexpression of carboxypeptidase-D (CPD) has been observed to be concurrent with high-grade lung cancer. Furthermore, it has been demonstrated that the inhibitory effects of miR-214 can be reversed by the overexpression of CPD [72].

Moreover, it has been shown that miR-214 exerts a crucial function in the pathogenesis of lung cancer by suppressing invasion and migration *via* targeting oncogenic JAK1 [61]. The inhibition of migration and invasion was observed in bladder cancer cell lines upon the reinstatement of miR-214 expression. The present investigation identified P53 And DNA Damage Regulated 1 (PDRG1) as a direct target gene of miR-214. The results indicate that miR-214 may have a tumor-suppressive impact on bladder cancer by directly reducing the expression of the oncogene PDRG1 [59]. While specific studies have supported the notion of miRNA-214 downregulation in cancer cells, several other studies have suggested the upregulation of this particular miRNA in cancer cells. The study revealed an up-regulation of miR-214 in GC9811-P cells, which possess a higher potential for peritoneal metastasis than GC9811 cells. Furthermore, the *in-vitro* amplification of miR-214 resulted in the enhancement of cellular invasion and migration capabilities of GC9811 cells, whereas the reduction of miR-214 had converse impacts in GC9811-P cells. In addition, the upregulation of miR-214 in GC9811 cells resulted in a significant decrease in PTEN expression, while the downregulation of miR-214 in GC9811-P cells led to a notable increase in PTEN expression. The results of this study suggest that miR-214 could potentially facilitate the peritoneal metastasis of GC cells by suppressing PTEN expression, ultimately contributing to the advancement of GC [62]. The authors Long et al. studied the role of miR-214 in lung adenocarcinoma. Their findings indicate that miR-214 significantly impacts the activation of the EMT process, ultimately promoting metastasis in lung adenocarcinoma. This effect is achieved by targeting suppressor-of-fused, a negative regulator of the Hedgehog signaling pathway [33]. Also, it is indicated that miR-214 exhibited a noteworthy upregulation in osteosarcoma and displayed an inverse association with TRAF3 expression. The study reports that overexpression of miR-214 significantly suppressed cell invasion and migration in osteosarcoma by targeting TNF receptor-associated factor 3 (TRAF3), as evidenced by the observed outcomes [42].

4.4. Stemness

Numerous miRNAs have been documented to exhibit anomalous expression in cancer and exert significant functions in cancer stemness. Qi et al. have demonstrated that miR-214 promotes cell self-renewal by directly targeting catenin beta interacting protein 1 (CTNNBIP1), a constituent of the Wnt signaling pathway. The authors exhibited that the overexpression of miR-214 amplifies the stem-like characteristics in lung adenocarcinoma cells. Additionally, miR-214 manifests escalated expression in cancer stem-like cells obtained from primary tumor tissue and two lung adenocarcinoma cell lines. Remarkably, the reduction of miR-214 expression in cancer stem-like cells led to a noteworthy decrease in the formation of spheroids and the expression of stem-cell markers Nanog, Oct-4, and Sox-2 [41]. The regulation of ovarian cancer stem cell properties through targeting the p53/Nanog axis was identified by researchers *via* miR-214. The augmentation of miR-214 expression resulted in an increase in ovarian cancer control cell population and self-renewal and a rise in Nanog level, particularly in cell lines with wild-type p53 [22,35].

Conversely, reducing miR-214 expression led to a decrease in the factors mentioned above. Additionally, it has been discovered that the tumor suppressor protein p53 is subject to direct repression by miR-214. Moreover, miR-214 is responsible for regulating Nanog *via* p53. The ovarian cancer stem cell properties induced by miR-214 were nullified by the expression of p53 [22,64].

4.5. Angiogenesis

The process of angiogenesis plays a crucial role in the progression of tumors and their spread to other parts of the body. Meanwhile, miRNAs serve as critical regulators of various biological processes, including angiogenesis and the formation of tumors. The microRNA miR-214 has been identified as a tumor suppressor in cases of human HCC, and its decreased expression has been linked to a poorer prognosis. The hypervascularity of HCC is attributed to the induction and secretion of hepatoma-derived growth factor (HDGF) resulting from the down-regulation of miR-214. The inhibition of tumor angiogenesis and subsequent suppression of tumor growth can be achieved through ectopic expression of miR-214 or HDGF antibodies as antagonists, as demonstrated in previous research [48]. Mil et al. have provided evidence indicating that miR-214 is a robust modulator of angiogenesis in both *in-vitro* and *in-vivo* settings, as demonstrated by manipulating miR-214 levels. The researchers discovered that miR-214 directly impacts Quaking (QKI), a protein crucial in vascular development and remodeling.

Additionally, miR-214 regulates the secretion of various angiogenic growth factors, including VEGF, bFGF, and PDGF [53]. The protein Constitutive photomorphogenesis 1 (COP1) is involved in the degradation of p53 *via* the proteasome, leading to the suppression of genes regulated by p53, including Bcl-2-associated X protein (BAX), Fas Cell Surface Death Receptor (FAS), Cyclin-dependent kinase inhibitor 1 A (CDKN1A, and Thrombospondin 1 (THBS), which are known to be activated by p53. The suppression of gene expression hinders programmed cell death, growth suppression, and anti-angiogenic effects. The induction of apoptosis is triggered by the inhibition of COP1-mediated degradation of p53 due to the up-regulation of miR-214, which directly targets COP1 [19].

4.6. Apoptosis

A study was conducted wherein flow cytometry was utilized to quantify the apoptosis of MCF-7 cells after the transfection of miR214–3p. The study's findings indicate that the apoptosis of MCF-7 cells transfected with miR-214–3p mimics was considerably increased with the extension of transfection time compared to the control group. Conversely, the apoptosis of MCF-7 cells transfected with miR-214–3p inhibitors was significantly inhibited compared to the control group. These results suggest that miR-214–3p may play a role in the apoptosis process [17]. Heishima et al. provided evidence that miR-214 plays a crucial role in regulating apoptosis by targeting COP1 in hemangiosarcoma. The dysregulation of p53 in hemangiosarcoma may be attributed to the down-regulation of miR-214 and the overexpression of COP1. Identifying miR-214 as a regulator of p53 signaling through the targeting of COP1 presents a significant opportunity to impede the hindrance of apoptosis [19].

According to a recent investigation, elevated levels of long non-coding RNA NEAT1 were found to facilitate the initiation of thyroid cancer. Furthermore, it has been demonstrated that NEAT1 promotes the malignant progression of thyroid cancer by modulating the expression miRNA-214, thereby contributing to the current knowledge of the molecular pathways involved in thyroid carcinoma [29,49]. The Mini-chromosome maintenance (MCM2–7) protein complex is a crucial constituent of the pre-replicative complex (pre-RC) and collaborates with other proteins to form a helicase that is responsible for the unwinding of the DNA duplex during the S phase. The overexpression of MCM proteins is a characteristic feature of cancer cells, whereas, in non-proliferating normal cells, their expression is strictly regulated and absent. According to reports, miRNA-214 can target MCM5 and MCM7. The expression of miR-214 is comparatively reduced in HepG2 and Hep3B hepatocellular carcinoma cells in contrast to the L-02 normal liver cells. The mRNA and protein levels of MCM5/7 were reduced, and DNA replication and cell cycle progression were inhibited in HepG2 and

Hep3B cells upon the introduction of miRNA-214 mimic [55].

The exosomal miR-214 originating from PC-9GR can induce gefitinib resistance in EGFR mutant lung cancer, achieved through inhibiting cell apoptosis *in-vitro* and suppressing tumor growth *in-vivo*. As such, it could be a promising therapeutic approach for treating gefitinib-resistant lung cancer [44]. Exosomal miR-214 derived from PC-9GR could confer gefitinib resistance in EGFR mutant lung cancer by suppressing cell apoptosis *in-vitro* and inhibiting tumor growth *in-vivo*, which may serve as a potential tool to treat gefitinib-resistant lung cancer [70]. In addition, it was observed that the expression of miR-214 was significantly elevated in both nasopharyngeal carcinoma tissues and cell lines. Subsequent examination revealed that the suppression of miR-214 impeded the process of cell proliferation and facilitated apoptosis in nasopharyngeal carcinoma cells.

In contrast, the upregulation of miR-214 was observed to stimulate the proliferation of nasopharyngeal carcinoma cells while concurrently suppressing cell apoptosis. The identification of Bcl-2-associated X protein (Bax) as a novel target of miR-214 was subsequently established. The protein expression of Bax was found to be negatively regulated by miR-214 in cells of nasopharyngeal carcinoma. The inhibition of Bax through siRNA was observed to mitigate the promoting impact of miR-214 downregulation on apoptosis in nasopharyngeal carcinoma cells. This finding indicates that Bax is a downstream effector in the miR-214-mediated cell proliferation and apoptosis regulation in nasopharyngeal carcinoma [18].

Furthermore, an additional investigation demonstrated that the restraint of miR-214 impedes cellular proliferation and prompts programmed cell death in nasopharyngeal carcinoma. MiR-214 regulated the expression of Phosphatase and tensin homolog (PTEN) and WW domain-containing oxidoreductase (WWOX) by targeting the 3'-UTR. The promotion of WWOX and PTEN expression, inactivation of the AKT signaling pathway, and regulation of cell-cycle- and apoptosis-associated proteins were observed upon inhibition of miR-214. The inhibition of miR-214 was observed to impact AKT signaling, cell proliferation, and apoptosis, subsequently reversed upon the knockdown of PTEN or WWOX [16].

5. Diagnostic and prognostic value of miRNA-214

Timely detection enables efficacious and comprehensive management of GC before progressing into a metastatic and advanced phase. Investigators are trying to discover convenient, non-invasive, highly sensitive, and highly specific biomarkers for early cancer diagnosis [52]. MiRNAs have the potential to serve as molecular therapeutic targets or diagnostic/prognostic biomarkers, depending on whether they function as a disease-driving force or accompanying feature [69]. MicroRNA-214 has been identified as a significant circulating miRNA, and its serum expression has demonstrated diagnostic significance. The study evaluated the expression of serum miR-214 in a cohort of 100 breast cancer patients and found that it could differentiate between advanced-stage tumors and early-stage tumors, as well as healthy individuals. The study reported a noteworthy reduction in expression levels in sera obtained post-operatively. However, an association was observed between elevated expression levels and the occurrence of distant organ metastasis and spread to regional lymph nodes [45]. Analogously, it has been noted that exosomal miRNA-214 in circulation exhibited upregulation in the primary tumor mass obtained from individuals with ovarian carcinoma, and a similar finding was observed in patients with lung cancer [63].

Additionally, it has been identified that the presence of urinary cell-free miR-214 holds promise as a biomarker for categorizing tumors, timely detection, and prognostic evaluation of bladder cancer [58]. Furthermore, Wang and colleagues have documented that extracellular miR-214 in serum could serve as a promising non-invasive biomarker for the classification, timely identification, and prognostic assessment of glioma patients [20]. The utilization of circulating miR-214–3p as a non-invasive biomarker has been demonstrated to be a viable approach for predicting recurrence or metastasis in patients with nasopharyngeal carcinoma. In addition, the surveillance of miR-214–3p in circulation holds promise for assessing the clinical course and therapeutic efficacy of nasopharyngeal carcinoma [57].

6. Conclusion and future direction

The field of non-coding RNAs (ncRNAs) underwent a significant transformation in 1993 with the discovery of miRNAs. Subsequently, extensive research has been conducted to comprehend the regulatory roles of miRNAs in various health conditions. The modulation of miRNA expression levels presents a potential avenue for cancer treatment. Two strategies for the development of miRNA-based therapeutics include miRNA replacement therapy, which involves the use of miRNA mimics to restore tumor suppressor gene function, and miRNA antagonists (antagomirs), which are synthetic RNAs that bind to specific miRNAs and inhibit their function, thereby enabling the translation of their target mRNA. The utilization of miRNA-based therapeutics presents a promising approach for targeted cancer therapy; this is due to the ability of a single miRNA to regulate multiple downstream genes by controlling a specific function or mechanism. MiR-214 influences various cellular functions through a diverse range of targets. Frequently, particular targets are assigned divergent roles. Consequently, it is of utmost importance to conduct a screening process to identify additional targets of miR-214, as this may uncover numerous unexplored roles in seemingly disparate medical conditions. Further *in-vivo* and *in-vitro* investigations are necessary to determine the underlying factors that determine whether miR-214 functions as a tumor suppressor or promoter.

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Declaration of Competing Interest

The authors declare they have no conflict of interests.

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