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REVIEW ARTICLE

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Diagnostic biomarker and therapeutic target applications of miR-326 in cancers: A systematic review

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Abstract

MicroRNAs (miRNAs) are endogenous mediators of RNA interference and have key roles in the modulation of gene expression under healthy, inflamed, stimulated, carcinogenic, or other cells, and tissues of a pathological state. Many studies have proved the association between miRNAs and cancer. The role of miR-326 as a tumor suppressor miRNA in much human cancer confirmed. We will explain the history and the role of miRNAs changes, especially miR-326 in cancers and other pathological conditions. Attuned with these facts, this review highlights recent preclinical and clinical research performed on miRNAs as novel promising diagnostic biomarkers of patients at early stages, prediction of prognosis, and monitoring of the patients in response to treatment. All related publications retrieved from the PubMed database, with keywords such as epigenetic, miRNA, microRNA, miR-326, cancer, diagnostic biomarker, and therapeutic target similar terms from 1899 to 2018 with limitations in the English language. Recently, researchers have focused on the impacts of miRNAs and their association in inflammatory, autoinflammatory, and cancerous conditions. Recent studies have suggested a major pathogenic role in cancers and autoinflammatory diseases. Investigations have explained the role of miRNAs in cancers, autoimmunity, and autoinflammatory diseases, and so on. The miRNA-326 expression has an important role in cancer conditions and other diseases.

KEYWORDS

cancer, diagnostic biomarker, epigenetic, miR-326, miRNAs, therapeutic target.

1 | INTRODUCTION

Cancer is categorized as the third leading cause of death worldwide next to cardiovascular and infectious diseases (Paranjape, Slack, & Weidhaas, 2009). In recent years, many studies have been focused on the diagnosis, treatment, and prognosis of cancer in the aspect of genetic and epigenetic factors. Epigenetic modulations are mostly based on DNA methylation, histone posttranslational modifications, and noncoding RNAs, especially the miRNAs. MiRNAs are a member of a broad family of noncoding RNA and can be as potential tumor suppressors or oncogenes. MiRNA genes are widespread in all of the genomes, excluding for chromosome Y, and are considered as a molecular tool for noninvasive diagnosis and prognosis of cancers (Filipow & Laczmanski, 2019). Summarily, modulation of gene expression by miRNAs occurs through the specific pairing of the miRNA sequence to its corresponding target messenger RNA (mRNA). This pairing can drive to either translational suppression or rupture of the mRNA, following in the decreased levels of the target protein. While hallmarks of cancer were reported and miRNAs were involved as major players in the management of all cancer hallmarks, there has been rising concern in targeting miRNAs as treatment of cancer, since 2011 (Cortez et al., 2019).

The wrong expression of miRNAs is often found in cancer, resulting in dysregulation of genes expression that regulates the biology of cancerous cells. miRNAs are classified as oncogenic miRNAs (oncomiR) which cause cancer by targeting antiproliferative, cell differentiation and proapoptotic genes, and tumor suppressive miRNAs that decrease in expression during cancer and modify the expression of the prosurvival, cell cycle, and proproliferative genes. Surprisingly individual miRNA can play a dual role as oncogenic or tumor suppressor in certain tumors, depending on cellular conditions. (Monteleone & Lutz, 2017). Both types of miRNAs associated with various biological processes such as metastasis and invasion in cancer, thereby implying that miRNAs might serve as new biomarkers for the diagnosis and molecule-targetted therapy of cancers (J. Y. Wang & Chen, 2019).

Many miRNAs have been reported as diagnostic biomarkers due to their dysregulation in cancers compared with normal tissue. Perhaps by the discovery of noninvasive methods, it is not necessary for biopsy and imaging to diagnose and treatment management of cancer patients. Accordingly, studying the function of miRNAs in regulating the immunity of cancer is important, and it can lead to the knowing of mechanisms that will lead to the discovery of new therapies in cancer patients.

It has been performed that miR-326 expression dysregulation associates in a variety of pathological process, including autoimmune diseases and cancers. Of course, its effects in biochemical markers of bone turnover in lung cancer bone metastasis and non-small-cell lung cancer (NSCLC) metastatic have also been described (C. Sun et al., 2016). Recent studies show that miR-326 could potentially use as a new biochemical marker for monitoring lung cancer bone metastatic progression (Valencia et al., 2013) and is an effective tool for preventing and reversing MDR in tumor cells (Liang et al., 2010). There are many factors involved in the development of cancer, but in this review, we will focus on the effects of miRNAs, in particular, miR-326.

2 | MIRNAS

MicroRNAs (miRNAs) are known as small, noncoding RNAs with almost 20–24 nucleotides in length that are associated with posttranscriptional regulation of gene expression and cell signaling. A single miRNA may regulate the several genes expression and also several miRNAs may affect a single mRNA. Their role in normal physiological processes is well-known, thereby dysregulation of miRNAs is assumed as key phenomena in carcinogenesis (Jadideslam et al., 2018).

Mechanisms of malignant transformation by miRNAs includes cell death resistance (miR-34-a, miR-15/16, let-7), tumor-promoting inflammation (miR-23b, miR-155, let-7d), deregulation of cellular energetic (miR-23a/b, miR-15b, miR-210), genetic instability (miR-21, miR-15b, miR-155), and evading immune surveillance (miR-124, miR-155, miR-17–92). In addition, miRNAs are able to modify processes like tissue invasion and metastasis (miR-200 family, miR-21, miR-15b), the unlimited replication potential (miR-21, miR-221/222, miR-16, let-7 family), insensitivity to antigrowth signal (miR-25, miR-95, miR-17–92), self-sufficiency (miR-21, miR-7, let-7), and sustained angiogenesis (miR-125, miR-15b, miR-155, miR-210; Salimi-Asl, Mozdarani, & Kadivar, 2016; Shah, Ferrajoli, Sood, Lopez-Berestein, & Calin, 2016).

MiRNAs were defined in *Caenorhabditis elegans* by Ambros and Ruvkun for the first time in 1993; they introduced Lin-4 as the first miRNA identified in *C. elegans*. The second miRNA reported as let-7 in 2000 which was ascertained to be conserved across the species that encouraged miRNA detection studies and quickly much more miRNAs were discovered in *C. elegans*, *Drosophila melanogaster* and human genomes. Humans have almost 2,000 annotated miRNA sequences and 24,521 miRNA loci annotated in 206 species (Rani, 2017).

More than half of the identified human miRNAs are located in fragile sites and genomic regions that are involved in cancer. It has been shown that the copy numbers of miRNAs are commonly abnormal in human cancers according to high-resolution array-based comparative genomic hybridization data. However, the mechanisms of only a few miRNAs are studied so far. Dysregulation of miRNAs may be inducible by epigenetic alterations, genomic deletion, genomic amplification, retroviral insertion, mutagenesis, a single nucleotide replacement resulting from a mutation or single-nucleotide polymorphism (SNP), and improper activation or inhibition of the proteins that directly control miRNA expression (Ying, 2008).

2.1 | Biogenesis of miRNAs

The sequences that encode miRNAs are normally transcribed by RNA polymerase II and processed by RNase III enzyme Drosha to form an approximately 70 nucleotide precursor miRNAs which are maturated in the, and their length is reduces to about 22 nucleotides. After maturity, miRNAs are able to identify the mRNA seed sequence and inhibit their expression (S. Wang, Wan, & Ruan, 2016).

2.2 | Roles of miRNAs

MiRNAs are bonded to the 3′-untranslated region (3′-UTR) of mRNA to regulate the specific target proteins expression via suppressing translation or degradation. Dysregulation of miRNAs expressions is reported in several human cancers that is tightly connected to almost all aspects of cancer biology, including differentiation, proliferation, apoptosis, metastasis, invasion, and angiogenesis (Fallah et al., 2019).

This review will summarize the current understanding of miR-326 regulation at the molecular level, focuses on its important role in development, metastasis, and oncogenesis, discusses its use as a diagnostic and prognostic biomarker and ultimately, defines its potential strategy in screening and treatment of diverse types of cancers (Y. Gao, Lin, Li, Yang, & Wei, 2017).

2.3 | MiRNAs and cancer

Many miRNAs affect the main regulatory molecules of the malignant cells and are involved in a complex signaling network among malignant cells and the tumor microenvironment (Rupaimoole, Calin, Lopez-Berestein, & Sood, 2016). The correlation between miRNAs and cancer was first introduced by G. Calin et al. in 2002 (Nikitina, Urazova, & Stegny, 2012). Subsequently, many studies have conducted on the effects of miRNAs in all aspects involved in cancer such as carcinogenesis, genomic instability, cell proliferation, apoptosis, replicative potential of cancer cells, regulation of angiogenesis, immune responses, tumor development, progression, tumor invasion and metastasis, drug resistance, prognosis, and so on (Nikitina et al., 2012; Ruan, Fang, & Ouyang, 2009; Figure 1).

3 | MIR-326 ROLE IN CANCER

The sequence encoding of miR-326 located within intron 1 of chromosome 11. MiR-326 has 20 nucleotides and is first recognized as a neural-specific miRNA in neurons. According to studies conducted so far, miR-326 has an important regulatory role in processes such as: cellular growth, proliferation, metabolism of glucose and lipid; dendritic cell function, acute rejection after heart transplantation immune cell lineage obligation; maturation, differentiation, maintenance of immune homeostasis; normal function, and as well as TH-17 differentiation (Jadideslam et al., 2018). Also, multiple investigations have confirmed that miR-326 is involved in embryonic development, immune response, inflammation, oncogenesis, invasion, metabolism, cell apoptosis, tumor growth, chemotherapy resistance, and autophagy (Jadideslam et al., 2018; Oghbaei, Ahmadi Asl, Sheikhzadeh, Alipour, & Khamaneh, 2015; Zununi Vahed et al., 2018).

Fascin1 (FSCN1) is the main target of miR-326 which regulates cell proliferation, metastasis, and low expression of miR-326 is associated with malignant status and poor prognosis in gastric cancer patients by FSCN1 targeting (Jadideslam et al., 2018). MiR-326 has a central role in NSCLC through inhibiting cell proliferation, migration, invasion, and promoting apoptosis by targeting oncogenic CCND1 (C. Sun et al., 2016). MiR-326 upregulates the expression of antifibrotic genes such as Smad7, while downregulating of profibrotic genes such as Ets-1 and matrix metalloproteinase-9 (Das et al., 2014). MiR-326 is an important guard of the epithelial phenotype by inhibiting transforming growth factor β1 expression (Zou, Liu, Gong, Hu, & Zhang, 2016).

Most recently, much evidence is showing miR-326 involvement in development and progression of neoplasia states as a tumor suppressor, such as colorectal cancer (G. Chen et al., 2016; Wu et al., 2015), NSCLC (R. Wang, Chen, & Shu, 2015), lung cancer (Cai et al., 2015), and glioma and brain cancer (Khan, Ullah, Hussein, & Saini, 2017). Also, it is involved in breast cancer (Liang et al., 2010), prostate cancer (Kristensen et al., 2016), esophageal cancer (Hong et al., 2014), cutaneous T-cell lymphoma (CTCL; Ralfkiaer et al., 2011), gastric cancer (Y. Li, Gao, Xu, Ma, & Yang, 2015), pancreatic ductal adenocarcinoma (Z. L. Zhang et al., 2015). Moreover, it intervenes in hepatocellular carcinoma (S. Hu, Ran, Chen, Zhang, & Xu, 2017), medulloblastoma (Ferretti et al., 2008), acute myeloid leukemia (AML; Koutova et al., 2015), chronic myeloid leukemia (CML; Babashah et al., 2013). Additionally, miRNA dysregulation also is seen in endometrial cancer (Torres et al., 2012), ovarian cancer (Nakamura et al., 2016), cholangiocarcinoma (Han et al., 2017; Jiao

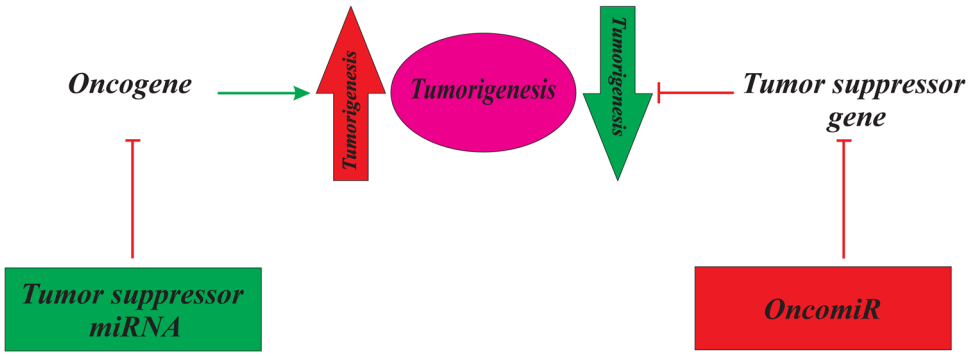

FIGURE 1 The schematic picture describing the pathways in which oncogenes can progress, and TSG can reduce the potential of tumor formation. A tumor suppressor miRNA would suppress an oncogene's function, and conversely, an oncomiR miRNA would suppress a TSG gene's function. miRNA: microRNA; OncomiR: oncogenic miRNA; TSG: tumor suppressor gene [Color figure can be viewed at wileyonlinelibrary.com]

et al., 2017; Meng et al., 2006; H. Zhu et al., 2017), chronic lymphocytic leukemia (Balatti, Pekarky, Rizzotto, & Croce, 2013; Bruns et al., 2017; Mraz et al., 2009), hepatitis C virus (HCV; Y. Chen et al., 2013; N. El-Ekiaby et al., 2012; N. M. El-Ekiaby et al., 2017; El Sobky et al., 2016; Estrabaud et al., 2015; Khanizadeh et al., 2017; Mahdy et al., 2016; Niu et al., 2016; Oksuz et al., 2015; Ono et al., 2017; Van Renne et al., 2017; G. Xu et al., 2014), influenza virus (Ingle et al., 2015; Y. Li et al., 2010, 2011; Rosenberger et al., 2017; X. Zhang, Dong, et al., 2014; Table 1 and Figure 2).

miR-326 acts as a tumor suppressor which regulates gastric cancer cells growth, migration, and invasion (Y. Li et al., 2015). Also, it may be efficient factors for preventing and reversing adriamycin (ADM) resistance in cancer cells (J. Ma et al., 2015).

Obviously, miRNAs interact with long noncoding RNAs (lncRNAs) in the pathogenesis of many cancers. For example, UCA1~miR-143, DLEU1~miR-19a, PVT1~miR-200, HOTAIR~miR-7, LINC00478~let7c, H19~miR-675, HOTAIR~miR-568, ROR~miR-205, GAS5~miR-21, LOC554202~miR-31 in breast cancer, BANCR~miR-9, HOTAIR~miR-152, MEG3~miR-148a, HOTAIR~miR-331-3p, TM4SF5~miR-4697-3p, CTD-2354A18.1~miR-4697-3p, TUSC7~miR-23b, H19~miR-141, H19~miR-675, ANRIL~miR-99a, ANRIL~miR-449a, GAPLINC~miR-211-3p, NCR143/145~miR-143/145, AC130710~miR-139-5p, linc-NR_024015~miR-526b in gastric cancer and so on (Nair, 2016).

3.1 | Colorectal cancer (CRC)

A recent study on 114 CRC indicated that miR-326 acts as a tumor suppressor in cancer cells and inhibits cell proliferation, migration, invasion, and induces cell apoptosis, carcinogenesis, and progression. MiR-326 suppresses cell cycle by targeting nin one binding protein (NOB1). Also, its low expression is associated with metastasis and recurrence risk of colorectal cancer and causes decreased survival rate in CRCs. miR-326 and NOB1 may act as a prognostic biomarker and potential therapeutic targets for CRC (Wu et al., 2015). In contrast, G. Chen et al. (2016) by analyzing the tissue samples from 14 people, concluded that miR-382, miR-217, miR-21, miR-1184, miR-326, and miR-330-5p would contribute to the CRC development by affecting *PITX2*, *VSNL1*, *TCF4*, *MEF2C*, and *FOS*. Bioinformatic analysis by Kou, Qiao, and Wang (2015) revealed that miR-326 can be utilized as a potential theragnostic target for CRC. A study by Kjersem has confirmed that miR-326 associated with both shortened progression-free survival (PFS) and overall survival (OS) between the two responders ($n = 90$) and nonresponders ($n = 60$) groups of metastatic colorectal cancer (mCRC) patients (Kjersem et al., 2014). According to a study done by Ahmed et al. (2009) on Stool and tissue samples of 15 patients and five controls, it is revealed that the amount of miR-326 is increased in stool specimen of the patients and maybe acts as an informative screening test.

3.2 | Lung cancer

NSCLC is common and accounts for about 80% of lung cancer and lung adenocarcinoma (LAC), is the primary kind of NSCLC. Wang et al. studies on 46 nude mice of the BALB/c strain and frozen NCI-H460 cells, determined that the expression of miR-10b, miR-144, miR-9, miR-31, miR-34b miR-25, miR-92a, miR-202, and miR-326 varies from the metastatic NSCLC and nonmetastatic tissues, which may provide a potential candidate for diagnosis, prognosis, and treatment (R. Wang, Chen, et al., 2015). CCND1 oncogene has an opposite correlation with miR-326 in NSCLC patients and inhibits cell proliferation, migration, invasion, and promotes apoptosis (C. Sun et al., 2016). miR-326 is able to mimic the inhibitory effects of NSBP1 inhibitor, which significantly suppresses NSCLC cell proliferation and invasion (D. Li, Du, et al., 2016). Also,miR-326 is correlated with biochemical markers of bone turnover in bone metastasis of lung cancer (Valencia et al., 2013). miR-326 indicates tumor suppressive activity and is decreased in lung cancer to control cell proliferation and metastasis in lung cancer by targeting Phox2a which is conducted by HOTAIR (R. Wang, Chen, et al., 2016). Also, according to a study by J. Zhu et al. (2016) on 129 participants, it was noticed that miR-25, miR-21, miR-27b and miR-326 can consider as the most promising biomarker for LAC (J. Zhu et al., 2016). MiR-326 upregulates epithelial-to-mesenchymal transition (EMT)-induced cells invasion in LAC by targeting of ADAM17 (Cai et al., 2015). It is proposed that miR-326–Gli2/Smo feedback loop regulates Sonic hedgehog (Shh) activity and may be involved in lung development and disease establishment (Jiang, Cushing, Ai, & Lu, 2014). HOTAIR/miR-326/SP1 pathway controls the chemoresistance of LAC cells (J. Li, Li, et al., 2016). X. Xu et al., (2017) studied the Human lung cancer cell lines and concluded that miR-30a-5p and BCL-2 would change the cancer therapy resistance.

3.3 | Brain cancer

Brain cancer is one of the most dreadful known cancers due to its low survival rate, high rate of resistance to therapy, relapse, and terrible neurological degeneration. Malignant and nonmalignant brain tumors are the most common type of tumors under the age of 20 (Sonali et al., 2018). Ferretti et al. (2008) by examining human and animal tissue samples and evaluation of D283 MB cell lines have shown that miRNA-mediated control of the Hedgehog (Hh) signaling pathway is involved in malignancy establishment and miR-324-5p, miR-125b and miR-326 besides Smoothened (Smo) and Gli factors (Gli1), inhibit cell growth and indicate tumor suppressive effect.

3.4 | Glioma

Glioblastoma (GB) is an aggressive astrocytoma. MiR-326 is reported to be decreased in GB compared with normal brain tissue, it has been confirmed to control the development of cerebellar neural progenitor and cancer cells initiation and progression. Recently, it was reported that miR-326 has a low level of expression in glioblastoma tissues and possibly regulates the metabolic activity of glioma and glioma stem cells, suggesting the participation of miR-326 in tumorigenesis and progression of glioma (S. Wang, Lu, et al., 2013). downregulation of miR-326 may be considered as the potential marker for predicting clinical outcome for advanced glioma patients, offering miR-326 as a

TABLE 1 MiRNAs associated with common human diseases

Malignancy	miRNA involved	References
Colorectal cancer	miR-1, miR-9, miR-10a, miR-17, miR-17-3p, miR-17-5p, miR-19, miR-21, miR-23a, miR-25, miR-26, miR-26a, miR-28-5p/-3p, miR-29-b2, miR-30a-3p, miR-30a-5p, miR-30c, miR-31, miR-32, miR-34s, miR-96, miR-99, miR-106m, miR-124b, miR-125a, miR-125b, miR-126, miR-128b, miR-133b, miR-135b, miR-137, miR-135b, miR-139-5p, miR-143, miR-145, miR-150, miR-183, miR-200a, miR-200b, miR-200c, miR-205, miR-214, miR-217, miR-223, miR-224, miR-326, miR-330-5p, miR-382, miR-494, miR-552, miR-592, miR-1184, let-7a-1, let-7b, let-7g	Almeida et al. (2012); G. Chen et al. (2016); Y. Ma, Zhang, et al. (2012); Oberg et al. (2011); Paranjape et al. (2009); Pichler et al. (2014); Ruan et al. (2009); Sanchez-Mejias and Tay (2015); H. B. Sun et al. (2014); Wu et al. (2015); Zhou et al. (2013)
Non-small cell lung cancer	miR-9, miR-10b, miR-16, miR-17, miR-21, miR-25, miR-31, miR-34b, miR-92a, miR-101-3p, miR-126, miR-140-5p, miR-144, 146a-5p, miR-146b-5p, miR-150-5p, miR-202, miR-205, miR-326, miR-376a, miR-451, miR-486, miR-661, miR-675	Balca-Silva et al. (2012); Cao et al. (2017); Feng, Yang, Hu, Wang, and Liu (2017); Flamini, Jiang, and Cui (2017); F. Gao et al. (2015); Goto et al. (2017); Huang, Sun, Wang, He, and Li (2015); D. Li, Du, Liu, and Li (2016); Y. Li, Zhang, Li, et al. (2017); F. Liu, Cai, et al. (2017); W. Lu, Zhang, et al. (2017); Sromek et al. (2017); R. Wang, Chen, et al. (2015); Y. Wang, Cong, et al. (2017); Xiang, Hang, Che, and Li (2015); Yuwen, Sheng, Liu, Wenyu, and Shu (2017); X. Zhang, He, et al. (2017); J. Zhao et al. (2015); Z. Zhao, Lv, Zhang, Zhao, and Lv (2017); W. Zheng, Zhou, et al. (2017)
Lung cancer	miR-17–92, miR-21, miR-25, miR-30, miR-31, miR-34, miR-34b, miR-126, miR-129, miR-138, miR-155, miR-181a, miR-189, miR-200b, miR-210, miR-218, miR-224, miR-326, miR-381, miR-545, miR-1180, let-7a	Cai et al. (2015); E. G. Chen, Zhang, Xu, Zhu, and Hu (2017); P. Chen, Zhao, and Li (2017); Du et al. (2014); He et al. (2017); W. W. Hu, Chen, et al. (2017); S. Li, Yang, Xia, Fan, and Yang (2017); X. X. Li, Liu, Meng, and Wang (2017); Y. Li, Zhang, et al. (2017); Naidu and Garofalo (2015); Ruan et al. (2009); L. Wang, Liu, Zhang, and Huang (2017); Yanaihara et al. (2006); You and Park (2017)
Brain cancer	miR-21, miR-221, miR-326	Khan et al. (2017); Ruan et al. (2009)
Glioma	miR-7, miR-9, miR-10a, miR-10b, miR-15a, miR-15b, miR-16, miR-19a, miR-20, miR-21, miR-23, miR-23a, miR-23b, miR-24, miR-25, miR-28, miR-31, miR-32, miR-33a, miR-34a, miR-34c, miR-92, miR-101, miR-106a, miR-124, miR-125a miR-125b, miR-128, miR-129, miR-130a, miR-130b, miR-136, miR-137, miR-142, miR-143, miR-145, miR-148, miR-152, miR-152-3p, miR-155, miR-181a-c, miR-195, miR-196a, miR-196b,miR-200a*, miR-204, miR-210, miR-216b, miR-221, miR-222, miR-253-5p, miR-326, miR-329, miR-330, miR-410, miR-451, miR-452, miR-483-5p,miR-483-5p, miR-489, miR-491-5p, miR-495, miR-520b miR-527, miR-584, miR-592, miR-617, miR-633, miR-634, miR-769-3p miR-884-5p	M. Chang, Qiao, et al. (2017); Cui et al. (2017); Guan et al. (2010); Khan et al. (2017); B. Li, Liu, Sun, et al. (2017); Y. Li, Ma, Wang, and Li (2017); Peng et al. (2017); Qin, Rong, Dong, Yu, and Yang (2017); Y. Wang and Wang (2017); T. Zhang, Ma, Zhang, Huo, and Zhao (2017); X. Zhao, Liu, et al. (2017)
Breast cancer	miR-7, miR-10b, miR-17–92 cluster, miR-19b, miR-21, miR-22, miR-242, miR-27, miR-27b, miR-29b-2, miR-30a, miR-30c, miR-31, miR-34a, miR-93, miR-101, miR-106a, miR-106b-25 cluster, miR-125a, miR-125b, miR-126, miR-128a, miR-135a, miR-144, miR-145, miR-146a/b, miR-150, miR-155, miR-181, miR-182, miR-183, miR-191, miR-199a, miR-200, miR-203, miR-205, miR-206, miR-210, miR-216, miR-221, miR-222cluster, miR-326, miR-328, miR-330, miR-335, miR-342, miR-373, miR-375, miR-451, miR-491, miR-512-3p, miR-520c, miR-608, miR-671, miR-767-3p, miR-769-3p, let-7	Chu et al. (2017); Heidary et al. (2015); Kovalchuk et al. (2008); Liang et al. (2010); Pan, Morris, and Yu (2009); Ruan et al. (2009); Sanchez-Mejias and Tay (2015); Sharma, Rajendran, Kulshreshtha, and Ghosh (2017); Tang, Ahmad, and Sarkar (2012); H. D. Zhang, Jiang, Sun, Li, and Tang (2017); K. Zhang, Zhang, Liu, Xiong, and Zhang (2014); L. Zhao, Zhao, He, and Mao (2017); H. Zhu et al. (2008)

(Continues)

TABLE 1 (Continued)

Malignancy	miRNA involved	References
Ovarian cancer	miR-17, miR-17–92 cluster, miR-19a-3p, miR-20a, miR-21, miR-23b, miR-25, miR-25-3p, miR-26a, miR-29a, miR-30a-5p, miR-92, miR-92a, miR-93, miR-106b, miR-122, miR-126, miR-132, miR-141, miR-145, miR-150, miR-150-5p, miR-152,miR-200a, miR-200b, miR-200c, miR-203, miR-205,miR-214, miR-221, miR-429, miR-645, let-7-b, let-7f, let-7i-5p	Nakamura et al. (2016)
Prostate cancer	miR-17, miR-19, miR-20a, miR-26, miR-101, miR-107, miR-125b, miR-185-5p, miR-195, miR-203, miR-214, miR-221-3p, miR-222, miR-326, let-7, let-7d	Bryant et al. (2012); Kristensen et al. (2016); Ruan et al. (2009); Sanchez-Mejias and Tay (2015)
Esophageal cancer	miR-30b, miR-92b, miR-126, miR-218, miR-302b, miR-326, miR-338, miR-655	P. Chang, Wang, Zhou, and Hou (2017); Hong et al. (2014); Jingjing, Wangyue, Qiaoqiao, and Jietong (2016); Kong et al. (2016); Q. Li, Zhang, Li, Liu, and Chen (2017); G. Ma, Jing, et al. (2017); Yan et al. (2017); M. Zhang, Zhang, et al. (2017)
CTCL	miR-155, miR-203, miR-205, miR-326, miR-663b, miR-711	Ralfkiaer et al. (2011)
Endometrial cancer	miR-99a, miR-100, miR-145, miR-199b-5p, miR-326,	Sanchez-Mejias and Tay (2015); Torres et al. (2012)
Gastric cancer	miR-17, miR-18a, miR-19a, miR-25, miR-30a, miR-31, miR-106a-5p, miR-133b, miR-139-5p, miR-181a-5p, miR-183, miR-195, miR-214, miR-326, miR-331-3p, miR-340, miR-378, miR-638	Ji et al. (2017); Y. Li et al. (2015); X. Liu, Song, et al. (2017); Z. Liu, Sun, et al. (2017); Paranjape et al. (2009); Sanchez-Mejias and Tay (2015); L. Y. Zhao, Tong, et al. (2017)
Pancreatic ductal adenocarcinoma	miR-15b, miR-25, miR-29b-2, miR-29c, miR-30c, miR-32, miR-95, miR-96, miR-100, miR-125b-1, miR-128b, miR-130b, miR-139, miR-141, miR-142-p, miR-146a, miR-148a, miR-148b, miR-155, miR-181a, miR-181c, miR-186, miR-196a, miR-200b, miR-214, miR-216, miR-217miR-222, miR-326, miR-345, miR-375, miR-376a	Paranjape et al. (2009); Z. L. Zhang et al. (2015)
Hepatocellular carcinoma	miR-18, miR-21, miR-34s, miR-122, miR-133a, miR-144, miR-199a, miR-224, miR-326, miR-372, miR-431	S. Hu, Ran, et al. (2017); Ruan et al. (2009); Sanchez-Mejias and Tay (2015)
Medulloblastoma	miR-30a, miR-125b, miR-323, miR-324-5p, miR-326, miR-367	Ferretti et al. (2008); Kaid et al. (2015); Singh et al. (2017); H. Zhang, Wang, and Chen (2017)
Cholangiocarcinoma	miR-16, miR-21, miR-106b, miR-141, miR-200b, miR-320	Han et al. (2017); Jiao et al. (2017); Meng et al. (2006); H. Zhu et al. (2017)
AML	miR-199b-5p, miR-301b, miR-326, miR-361-5p, miR-625, miR-655	Koutova et al. (2015)
CML	miR-21, miR-124-3p, miR-326, miR-424	Babashah et al. (2013); Hershkovitz-Rokah et al. (2015); Y. X. Liu, Wang, et al. (2016); W. Z. Wang, Pu, et al. (2015)
CLL	miR-15/16, miR-17-5p, miR-29, miR-29c, miR-34a, miR-155, miR-181	Balatti et al. (2013); Bruns et al. (2017); Mraz et al. (2009)
Melanoma	miR-25, miR-92a, miR-181, miR-200b	Sanchez-Mejias and Tay (2015)
Lymphoma	miR-30a, miR-182, miR-876	Sanchez-Mejias and Tay (2015)

Abbreviations: AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; CTCL: cutaneous T-cell lymphoma; miR: microRNA.

possible candidate tumor suppresive biomarker (S. Wang, Lu, et al., 2013). Kefas et al. discovered miR-326 targets Notch1/2 and pyruvate kinase M2 to decrease proliferation and invasion rate in different in vitro studies. Furthermore, it is suggested that miR-326 and Notch1 are controlling each other mutually by negative feedback. They also confirmed that overexpression of miR-326 induces apoptosis and suppresses proliferation, viability, invasiveness and in vivo tumor volume decrease, and it may be a capable target for GB therapy (Kefas et al., 2010). A recent study has shown the potential application of miRNAs profile and their interactions in the development and improvement of prognostic tools and treatments of GB (Qiu et al., 2013). SOS1, NRAS, VDR, SMAD3, SGMS1, and HPGDS are considered targets of miR-326 for regulating of cancer promotion (X. Liu, Song, Li, Wang, & Yang, 2017). Furthermore, high

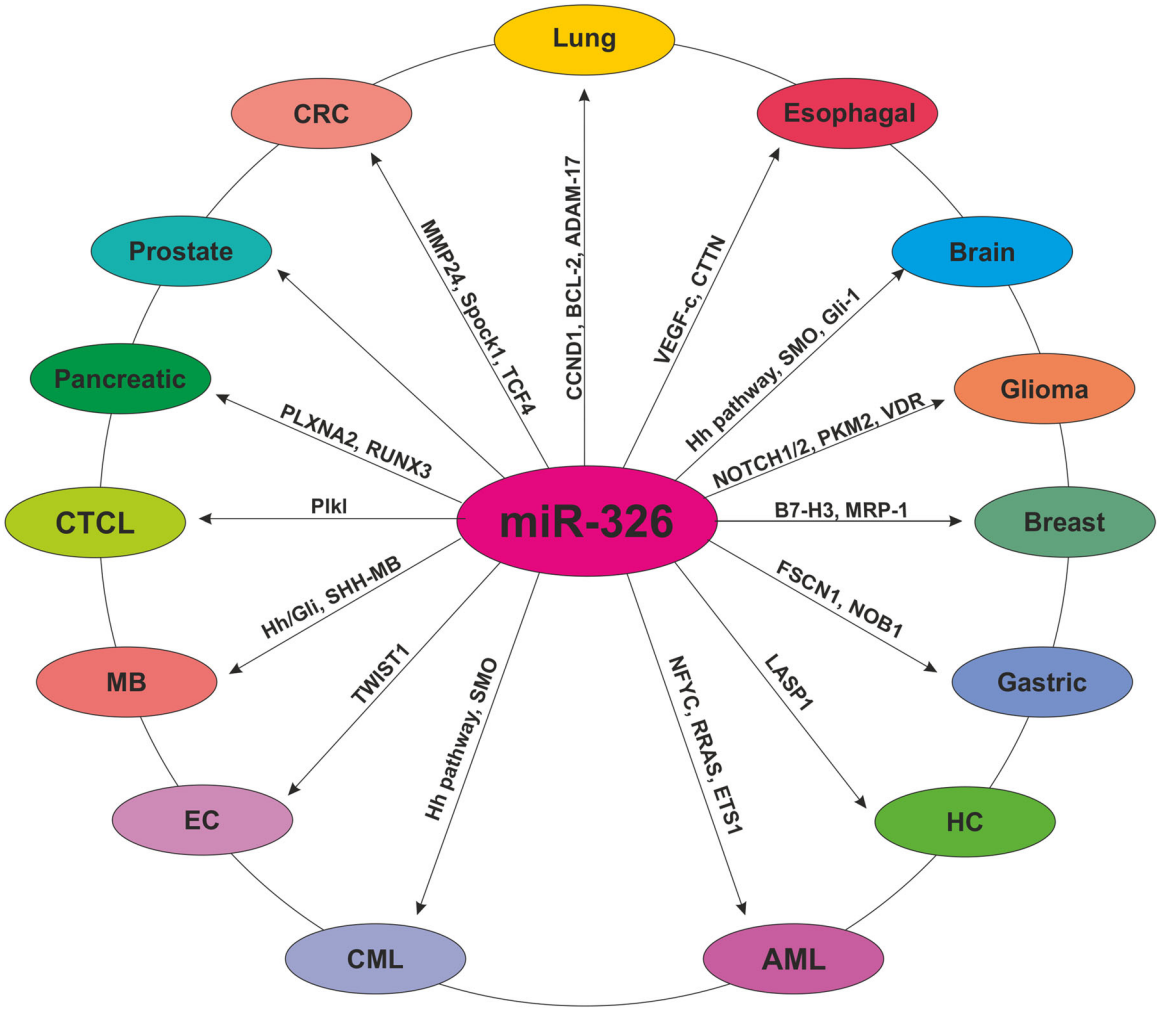

FIGURE 2 A list of cancers involved with miR-326 with their possible targets. ADAM17: ADAM Metallopeptidase Domain 17; AML: acute myeloid leukemia; B7-H3: CD276 (an important immune checkpoint member of the B7 and CD28 families); BCL2: BCL2, apoptosis Regulator; CCND1: cyclin D1; CML: chronic myeloid leukemia; CRC: colorectal cancer; CTCL: cutaneous T-cell lymphoma; CTTN: cortactin; EC: endometrial cancer; FSCN1: fascin actin-bundling protein 1; HC: hepatocellular carcinoma; Hh pathway: hedgehog signaling pathway; Hh/Gli: hedgehog-Gli pathway; LASP1: LIM And SH3 Protein 1; MB: medulloblastoma; miR: microRNA; MMP24: matrix metallopeptidase 24; MRP-1: multidrug resistance-associated protein 1; NOB1: Nin one binding protein 1; NOCTH1,2: notch signaling pathway1,2; PKM2, pyruvate Kinase M2; SHH-MB: sonic hedgehog medulloblastoma; SMO: smoothened, frizzled class receptor; SPOCK1: SPARC (Osteonectin), Cwcv And Kazal Like Domains Proteoglycan 1; TCF4: transcription factor 4; VDR: vitamin D receptor; VEGFC: vascular endothelial growth factor C [Color figure can be viewed at wileyonlinelibrary.com]

mobility group AT-hook 1 (HMGA1) and HMGA2 genes are suggested as possible targets of miR-326 by bioinformatics approaches (D'angelo et al., 2012). Moreover, HOTAIR is the target of miR-326 which is a tumor suppressor, in HOTAIR knockdown glioma cell lines its overexpression decreases the fibroblast growth factor 1 (FGF1) expression which is an oncogene to stimulate PI3K/AKT and MEK 1/2 pathways. These results provided a comprehensive analysis of HOTAIR-miR-326-FGF1 axis and propose a new therapeutic strategy for the treatment of glioma (Ke et al., 2015).

3.5 | Breast cancer

Breast cancer is the most common cancer in women and is the second most common cancer in the entire population (Zare, Bastami, Solali, & Alivand, 2018). MiR-326 directly modulates B7-H3 by attaching to 3′-UTR region (Nygren et al., 2014). It is negatively correlated with multidrug resistance-associated protein-1 (MRP-1) expression in breast cancer cells and tissues (Liang et al., 2010).

3.6 | Prostate cancer

Prostate cancer (PC) is the most common men malegnancy and is the second leading cause of death worldwide (Jemal, Siegel, Xu, & Ward, 2010). Bryant et al. in a study on 78 patients with PC and 28 healthy control indicated that miR-107 and miR-326 concentration may represent a novel method for evaluating of PC (Bryant et al., 2012). Kristensen et al. (2016) indicated a specific miRNA signature (miR-185-

5p, miR-221-3p, miR-326) with significant independent prognostic value in PC patients.

3.7 | Esophageal cancer

Esophageal cancer is the seventh most common cancer worldwide, and the most common form of this cancer type is esophageal squamous cell carcinoma (ESCC; X. C. Wang, et al., 2012). Hong et al. (2014) have shown that miR-326 is associated with poor prognosis in esophageal cancer and it can be used as a biomarker for diagnosing and therapy. The effect of miR-326 is by corticin (CTTN), a regulator of the cortical actin cytoskeleton, and VEGF-C.

3.8 | Cutaneous T-cell lymphoma

The most common primary skin lymphomas are CTCL. According to recent studies by Ralfkiaer et al. (2011) on 200 subjects of CTCL, it is showed that miRNAs have a high diagnostic potential, for instance, miR-326, miR-663b, miR-711, miR-203, miR-205, and miR-155. They presented that a single miRNA panel could perform differential diagnosis between diseases such as benign inflammatory skin disorders and CTCL with very high accuracy.

3.9 | Endometrial cancer (EC)

EC is one of the most common malignancies in females, which indicating an increase in incidence. Liu et al. studied 56 EC patients and found that the expression of this miRNA is reduced in the EC cell lines and tissues, and its expression induces inhibition of proliferation and metastasis. They found that tumorigenesis of EC could induce a reduction in miR-326 expression and confirmed that miR-326 as a tumor suppressor that may be applicable as a target for diagnosis or therapy approaches (W. Liu, Zhang, Xu, Wang, & Liu, 2017).

3.10 | Gastric cancer

Gastric cancer is the second cause of mortality worldwide due to cancer (Kahroba, Hejazi, & Samadi, 2019). Recent studies have shown that miR-326 operated as a tumor suppressor in gastric cancer by directly regulating FSCN1 (Y. Li et al., 2015) and NOB1 (Ji, Zhang, Kong, Ma, & Hua, 2017). The results of a meta-analysis that studied the effects of miRNAs in gastrointestinal cancers (GIC) showed that 23 miRNAs significantly are upregulated and 36 miRNAs are significantly downregulated which are correlated with poor prognosis in GIC patients. They found that miR-326 and other miRNAs are possible diagnostic biomarkers for gastric cancer (Q. Zheng, Chen, Guan, Kang, & Yu, 2017).

3.11 | Pancreatic ductal adenocarcinoma (PDAC)

In PDAC patients, downregulation of miR-326 is highly associated with venous invasion, but upregulation of miR-326 is associated with a good prognosis for the patients. Therefore, miR-326 plays a protective role during PDAC carcinogenesis and progression. The high expression of miR-326 probably increases the survival rate by reducing the invasiveness of PDAC (Z. L. Zhang et al., 2015).

3.12 | Hepatocellular carcinoma (HCC)

HCC, the most common form of liver malignancy, is the fifth common cancer and is the third leading cause of cancer death. Recent studies indicated that miR-326 inhibits the progression of HCC by direct modulation of LIM and SH3 protein 1 (LASP1), which are targets of miR-326. Regarding the overexpression of miR-326 in HCC, it is consumed as a potential therapeutic target (S. Hu, Ran, et al., 2017). In addition, in a study by Leo et al., on 377 samples, it has been shown that miR-326 overexpression is correlated with a survival rate in HCC patients and can also be applied as a diagnostic biomarker of HCC (M. Lu, Kong, et al., 2017).

3.13 | Medulloblastoma

Medulloblastoma is known as the most common childhood primary brain malignancy. Recent studies showed that miR-326 is involved in the regulation of SHHMB cancer stem cells, and they confirmed that downregulation of the miR-326 triggers and maintains the Hh/Gli signaling activation and self-renewal in SHH-MBs (Miele et al., 2017). Also, targeting of Smo by miR-326 inhibits its function (Ferretti et al., 2008).

3.14 | Acute myeloid leukemia

AML is the most common hematologic malignancy in adults. According to studies in miRNAs filed on AML patients, it is showed that the rate of miR-326 in postchemotherapy patients is significantly reduced and for this reason, it is a follow-up candidate in the treatment of the AML (Baghbani et al., 2018; Koutova et al., 2015; Yazdani et al., 2019).

3.15 | Chronic myeloid leukemia

CML is a myeloproliferative disorder that begins primarily from a single transformed hematopoietic stem cell (HSC) or multipotent progenitor cell. Recently, according to a study conducted on the human myeloid cell lines (K-562 and HL60) and primary CD341 leukemic cells of patients, it has been shown that miR-326 activates Smo signal transducer of the oncogenic Hh pathway that induces relapse in CML (Babashah et al., 2013). In another study, the effects of some compounds on Smo pathway inhibition and their potential function to reduce cell proliferation and induce apoptosis/autophagy in both the tested cell lines (K-562 and in KU-812) are performed. It is found that these compounds were able to regulate some miRNAs, such as miR-324-5p, miR-155, and miR-326, and we may be able to use them as a good therapeutic target for CML (Chiarenza et al., 2016; Edalati Fathabad et al., 2017).

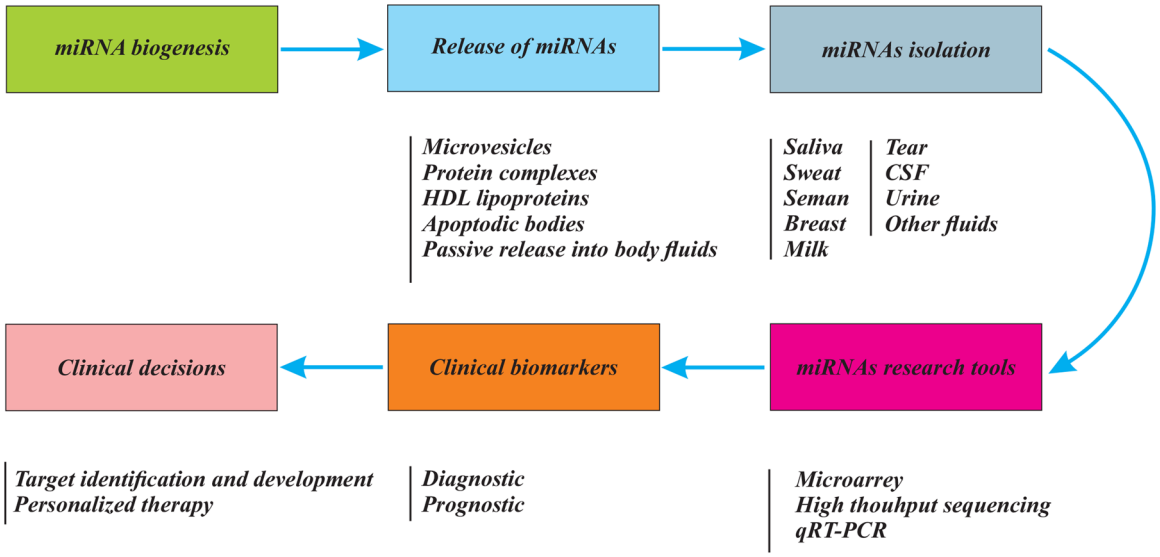

FIGURE 3 Schematic picture of miRNA biogenesis, methods of their secretion, miRNA extraction, and quantitative tools. In the future, a clinical decision-making strategy can be created for the targeted and personalized treatment of the disease. CSF: Cerbrospinal fluid; HDL: High density lipoprotein; miRNA: microRNA; qRT-PCR: quantitative reverse-transcription polymerase chain reaction [Color figure can be viewed at wileyonlinelibrary.com]

4 | MIRNAS IN STRATEGIES OF DIAGNOSIS

The several aspects of miRNAs which are capable for diagnosis of cancers include: using a signature of modified miRNA expression to distinguish cancer tissue from normal tissue, use of miRNA based classifier to recognize tissue of origin for cancers of unknown primaries, profiling circulating blood, or tumor deriver exosomal miRNAs, surpassing the invasive procedures to aid in early detection of cancers, distinguishing tumor subtypes using a panel of miRNAs that show differential expression within one cancer type and study SNPs in the miRNA genes, miRNA binding sites in the target mRNA genes or in the miRNA processing/machinery pathway genes to predict cancer predisposition (Paranjape et al., 2009).

5 | MIRNAS THERAPEUTICS STRATEGIES

MiRNAs are novel targets for cancer diagnosis and therapy (Paranjape et al., 2009). Currently, numerous RNAi-based strategies are defined for cancer therapy, for instance, sandwich RNAi inhibition strategy, multiplex RNAi inhibition strategy, miRNA inhibition therapy, miRNA mimetic agents, SMIRs-small molecules inhibitors of miRNAs and targeting miRNAs From microvesicles and exosomes (Aslan et al., 2019).

Novel strategies for inhibitory-miRNA treatments based on miRNA sponges, LNA-antimiR constructs, antisense antimiRs (LNA), and antagomiRs and effectiveness of someone confirmed in vivo and in vitro. Some studies have suggested mir-326 is capable to be used for the treatment of cervical cancer (Cheng, Jiang, Yuan, Liu, & Simoncini, 2018), diagnosis and detection of prognosis of pediatric ALL (Ghodousi & Rahgozar, 2018), diagnosis and treatment of osteosarcoma (J. Wang, Cao, Wu, & Wang, 2018). Now, many clinical trials have begun on the use of miRNAs in the treatment of diseases, especially, in the treatment of fibrosis, HCV infection, atherosclerosis, and cancer. However, more work must perform on miRNA delivery systems, an improvement in the stability of miRNAs, and a detailed knowledge of the off-target results of miRNA therapies (Eyvazi et al., 2019; Shah et al., 2016; Figure 3).

6 | CONCLUSION AND PERSPECTIVES

In brief, much evidence proposes that miR-326 acts as a critical regulator of different cancers, mainly through its targeting of related genes and collaboration with various signaling pathways. It can act as a tumor promoter or suppressor and is involved in many processes of cancer cells, including cell proliferation, apoptosis, differentiation, metastasis, and invasion. More studies with larger sample sizes are needed to clarify its questionable role in cancers. With regard to the miR-326 role in carcinogenesis, it could also applicate as a hopeful biomarker for diagnosis and differential diagnosis, prognosis evaluation and tumor staging. MiR-326 can be ideal for clinical use because it has stability characteristic. Most importantly, our recent knowledge of miR-326 can lead to the development of new therapies for cancer. In the near future, we have to recognize major miR-326 targets and by therapeutically modulate levels of this miRNA develop safe, accurate and specific methods, and it can be miR-326 one of the most important therapeutic targets for cancer therapy.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

G. J. contributed to design of the paper, data collection, draw the figures, and writing the paper. K. G., M. K., R. R. contributed to revise and analyzing the final version of the paper. Z. B. and A. A. contributed to data collection. K. A., E. S., A. K. contributed to design of the paper.

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