A brief overview of the role of microRNA-338 in carcinogenesis

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Abstract

MicroRNAs (miRNAs) are a class of short, non-coding RNAs that play an important role in a wide range of biological processes by directly binding to and repressing the expression of certain target genes in a post-transcriptional manner. More than one-half of human genes were controlled by miRNAs and their abnormal expression was discovered in different human illnesses, including malignancies. In recent years, researchers have discovered mounting evidence that the recently discovered miRNA miRNA-338 has a role in the development of a wide variety of malignancies, including lung cancer, hepatocellular carcinoma, breast cancer, glioma, and others. Although a number of targets and signaling pathways such as MACC1 and Wnt/β-catenin signaling pathway were revealed to be controlled by miRNA-338, their roles in tumor growth are still vague and the underlying molecular processes are still uncertain. In this article, we summarized the current state of knowledge on miRNA-338 and its activities in various human cancers in the hopes that this would spark fresh ideas for future research and the development of targeted therapies.

Keywords: MicroRNA-338, tumor suppression, proliferation, migration, and apoptosis.

1. Introduction

When it comes to public health concerns, the globe over, cancer ranks first. In 2018, it is predicted that 4.3 million new cases of cancer and 2.9 million new deaths from cancer would occur in China [1]. The global populations of these two groups in 2018 were 18.1 and 9.6 million, respectively [2]. In spite of the fact that significant work has been done over the last several decades to demonstrate the processes of carcinogenesis and certain tactics have truly had favorable impact on cancer therapy, there is still room for improvement. There is growing evidence that microRNAs (miRNAs) are important players in cancer development and may serve as diagnostic biomarkers or therapeutic targets.

MicroRNAs (miRNAs) are a kind of small, non-coding RNA (ncRNA) that are about 22 nucleotides in length and exhibit significant levels of conservation [3, 4]. They are involved in post-transcriptional control of human gene expression. They may construct the RISC (the RNA-induced silencing complex) with other protein components. RISC inhibits gene expression by identifying and binding to the 3′-UTR of target transcripts, resulting in degradation, translational repression, or direct mRNA cleavage [4]. More than 2600 miRNAs have been identified in the human genome, and it is estimated that miRNAs control between 30 and 50 percent of all functional genes [5, 6]. For example, the expression of cyclinD1 and cell-cycle progression might be suppressed by miRNA-206 in hepatocellular carcinoma [7], miRNA-708-3p lowers ZEB1 expression to limit breast cancer metastasis [8]. MiRNA-196a promotes cisplatin resistance by targeting CDKN1B in head and neck cancer [10], whereas miRNA-224 may enhance lung cancer...
metastasis by reducing TUSC3 expression [9]. These investigations showed that microRNAs play an essential regulatory function in numerous biological progressions and closely associated to the carcinogenesis.

The microRNA (miRNA) 338 has been linked to a wide variety of biological functions. Saba et al. (2008), in a study of prion-induced neurodegeneration, observed that its expression was considerably reduced in the brains of infected mice that had been modified to accept a scrape from a mouse [11]. Over the last several years, evidence has accumulated suggesting that miRNA-338 may play a crucial role in carcinogenesis by being dysregulated in a wide range of malignancies. Its role in carcinogenesis, however, remains debatable. MiRNA-338-3p, for instance, has been shown to accelerate the advancement of acute myeloid leukemia [12] and to prevent the progression of malignant melanoma [12] by targeting MACC1. Therefore, in this review, we examine the functions of miRNA-338 in various malignancies and discuss the mechanisms by which miRNA-338 controls carcinogenesis, with the hope that our findings may inspire new research and treatment approaches.

2. Expression of miR-338 is controlled

The miRNA-338 cluster, found in the intron of the apoptosis-associated tyrosine kinase (AATK) gene [14], encodes six distinct mature miRNAs (miRNA-338-5p, miRNA-338-3p, miRNA-3065-5p, miRNA-3065-3p, miRNA-657, and miRNA-1250). miR-338 situated inside AATK gene, is transcribed concurrently with AATK major transcript by the same promoter. In human neuroblastoma cells, for instance, retinoic acid has been shown to increase production of both miRNA-338-3p and its host gene AATK [15]. In addition, miRNA-338-3p also regulates AATK mRNA levels by binding to its 3′-untranslated region (UTR), and the miRNA-338 cluster (including miRNA-338-3p and miRNA-3065-5p) shows a consistent expression pattern throughout embryonic development in vivo. At embryonic day 9.5 (E9.5), both miRNA-338-3p and miRNA-3065-5p were expressed in the neural crest; they were also highly expressed in the limbs at embryonic days 10.5 and 11.5 [16]. Those with Alzheimer's disease have been shown to have elevated levels of miRNA-338-3p and miRNA-3065-5p in their plasma exosomes [17]. Furthermore, oligodendrocyte expression of miRNA-338, miRNA-1250, miRNA-657, miRNA-3065-5p, and miRNA-3065-3p was demonstrated to be identical [18].

Furthermore, it has been observed that the expression of miRNA-338-3p was lowered by the EGFR [19]. Furthermore, estrogens may suppress miRNA-338-3p in breast cancer by way of GPER [20]. In addition to making colorectal cancer resistant to chemotherapy, HIF-1 suppressed its expression by repressing the production of miRNA-338-5p [21]. E2H2 was also shown to be elevated in PCA patients, as reported by Bhatia et al. [22], which may have contributed to the epigenetic silencing of miRNA-338-5p. In addition, Tong et al. [23] discovered that MECP2 was downregulated in miRNA-338-3p and miRNA-338-5p expression due to its overexpression in GC. Furthermore, miRNA-338-3p was epigenetically silenced in GC tissues due to an increase in the methylation status of CpG islands in the promoter region [24]. More intriguingly, ceRNAs like lncRNAs and circRNAs may block miRNA-338 from interacting with its target genes (Fig. 1). For instance, LncRNA DSCAM-AS1 promotes the development of hepatocellular carcinoma by sponging miRNA-338-5p [25]. By controlling the miRNA-338-3p/FKBPIA axis, LncRNA-SNHG15 boosted PCA cell proliferation, migration, and EMT [26]. Glia cell proliferation, migration, and invasion were all boosted by CircRNA-SMO via miRNA-338-3p sponging [27]. CircRNA-MAT2B lowered the expression of miRNA-338-3p and enhanced glycolysis and aggressiveness of hepatocellular carcinoma [28]. Table 1 provides a summary of lncRNA-miRNA338 networks, while Table 2 does the same for circRNA-miRNA338 networks.

3.1. Non-small-cell lung cancer and microRNA-338

High morbidity and death rates make lung cancer the most common malignant tumor globally; more than 80% of lung cancer cases are NSCLC. The role of miRNA-338-3p as a tumor suppressor in NSCLC has been the subject of an increasing number of studies. miRNA-338-3p was shown to be considerably downregulated in NSCLC tissues and linked adversely with pathological stage and lymph node metastasis, as previously reported. Cell proliferation may be suppressed and apoptosis induced with the transient overexpression of miRNA-338-3p, which specifically targets IRS2,
RAB14, or SphK2 [68, 69, 70]. Also, by reducing the expression of epithelial-mesenchymal transition (EMT) regulator transcription factors SOX4 and ZEB2 [71, 72], miRNA-338-3p reduces NSCLC metastasis. Furthermore, miRNA-338-3p may target NFATc1 or NRPL1 to suppress NSCLC proliferation, EMT, invasion, and migration [73], [74].

Both circ-RNA and long non-coding RNA have been implicated in controlling miRNA-338 expression. Knockdown of lncRNA-CRNDE may enhance miRNA-338-3p expression, resulting in treatment that suppresses cell growth, as described by Jing et al. [30]. Additionally, LINC00525 inhibited miRNA-338-3p, which it subsequently used to boost IRS2 expression and advance NSCLC [31]. In addition to regulating the miRNA-338-3p/IRS2 axis, circ_0000003 [52]. Additionally, Has_circ_0000326 via the miRNA-338-3p/RAB14 axis boosted lung adenocarcinoma proliferation, migration, and suppressed apoptosis [51]. As a tumor suppressor, miRNA-338-3p was anticipated to play a pivotal role as a therapeutic target in lung cancer.

3.2. Hepatocellular carcinoma and microRNA-338

In terms of cancer-related mortality, hepatocellular carcinoma (HCC) ranks third globally and is the fifth most common malignant cancer overall. Huang’s study found that miRNA-338 expression was downregulated in HCC and adversely linked with tumor volume, clinical aggressiveness as well as node-metastasis [75]. Targeting FOXP4 [76] and SphK2 [77], as well as suppressing EMT and metastasis by targeting N-cadherin [78], miRNA-338-3p has been demonstrated to reduce cell proliferation in HCC. HCC angiogenesis was also inhibited by miRNA-338-3p, which did so by targeting the MACC1, VEGF, and catenin signaling pathway [79]. In addition, Jian et al. [54] found that has_circ_000092 may suppress miRNA-338-3p, boost HN1 expression, and advance HCC. miRNA-338-3p, via targeting HIF-1, has been shown to sensitize HCC cells to sorafenib [80], while miRNA-338-5p, by downregulating ABCB1, has been shown to sensitize HCC cells to doxorubicin and vinblastine [81]. Based on the results of these analyses, it seems that miRNA-338 may have a tumor-suppressing role and make HCC cells more amenable to anticancer treatment.

3.3. Cancer of the stomach and microRNA-338

High fatality rates and high incidence make gastric cancer (GC) a dreaded disease. MiRNA-338-3p is epigenetically repressed due to hypermethylation of its promoter region; restoring its expression inhibits cell metastasis and invasion [82]. Downregulation of miRNA-338-3p in gastric cancer tissues was inversely linked with higher clinical stage and lymph node invasion, according to a separate research [83]. In addition, Guo et al. [84] found that targeting P-REX2a with miRNA-338-3p suppressed cell proliferation in vitro and tumorigenicity in vivo via a PTEN-AKT axis. MiRNA-338-3p was shown to target PTP1B, NRPL1, EphA2, and the Wnt/-catenin signaling pathway, all of which have a role in GC's growth, invasion, and metastasis [85, 86, 87]. Interestingly, MECP2 also repressed the expression of miRNA-5p and miRNA-338-3p in GC, both of which target P-REX2 and BMI1 and have antiproliferation functions [23]. In conclusion, miRNA-338 has a specific tumor suppressive role in the development of GC, making it a desirable therapeutic target.

3.4. colorectal cancer

Another prevalent malignant tumor seen in the digestive tract is colorectal cancer (CRC). Recent research has linked miRNA-338 to the onset and progression of colorectal cancer (CRC). miRNA-338-3p was demonstrated to inhibit cell proliferation by repressing SMO expression [88]. Xue et al. further reported miRNA-338-3p may decrease CRC cell invasion and migration via the SMO inhibition [89]. In addition, Zhang’s study [43] showed the existence of a miRNA-338-3p/MACC1 axis, and the work of Zou et al. [90] demonstrated that miRNA-338-3p inhibited cell proliferation and prevented CRC advancement by targeting MACC1. In addition, circRAE1 encourages migration by altering the miRNA-338-3p/TYROID axis in CRC [60], while lncRNA-SNHG15 stimulates cell proliferation by sponging miRNA-338-3p and upregulating FOS or RAB14 [44]. These results suggested that miRNA-338-3p may have a tumor-suppressor role in colorectal cancer. However, it was found that miRNA-338-5p had cancer promoting effect in CRC, which
enhanced metastasis of colorectal cancer via inhibition of PIK3C3 [91]. And miRNA-338-5p was attributed to the oxaliplatin resistance of CRC in vivo by suppressing IL-6/STAT3/Bcl2 signaling pathway [21]. As a miRNA-338-5p sponge, has-circ-0137008 inhibits miRNA-338-5p-mediated enhancement of CRC cell progression [67]. It is clear from these findings that more research is required to elucidate the contrasting roles and mechanisms of miRNA-338-3p and miRNA-5p in CRC.

3.5. Cancer of the esophagus caused by squamous cell and microRNA-338

In Eastern Asia, men are disproportionately affected with esophageal squamous cell carcinoma (ESCC), a kind of malignant tumor. MiRNA-338-3p was shown to be downregulated in ESCC tissue relative to surrounding non-tumor tissue in a study by Li et al. Overexpression of miRNA-338-3p reduced migration, increased apoptosis, and slowed tumor development [92, all of which were connected with its low expression and the propensity for metastasis]. In ESCC, miRNA-338-3p was shown to inhibit CST3 expression, which in turn increased caspase-8/3 expression and triggered apoptosis [39]. In addition, LncRNA-BANCR promotes ESCC development by sponging miRNA-338-3p and activating the IGF1R/Raf/MEK/ERK pathway [40]. Importantly, there is mounting evidence that miRNA-338-5p has a role in chemoresistance in ESCC. Overexpression of miRNA-338-5p, as described by Park et al. [93], may cause apoptosis in ESCC cells and increase their radiosensitivity. In addition, downregulation of FERMT2 expression by miRNA-338-5p increased sensitivity of ESCC cells to cisplatin [94]. In conclusion, miRNA-338-3p and miRNA-338-5p were tumor suppressors and were likely to emerge as critical targets for overcoming ESCC’s resistance to radiotherapy and chemotherapy.

3.6. Breast cancer and microRNA-338

Worldwide, about one-fourth of all female cancers are diagnosed as breast cancer (BC), making it one of the most common tumor malignancies. The overexpression of EGFR in BC was linked to tumor aggressiveness and a poor prognosis. EGFR was discovered by Lia et al. [19] to inhibit the production of miRNA-338-3p, which targets EYA2 and inhibits EGFR-mediated breast tumor development and lung metastasis. Estrogens may also alter miRNA-338-3p expression in breast cancer (BC) cells and fibroblasts linked with cancer [20]. In addition, Zhang proven that circ_0008945 reduced miRNA-338-3p expression and consequently increased HOXA3 and tumor development [62]. Cell proliferation, migration, and invasion were all slowed or stopped by miRNA-338-3p’s direct downregulation of SOX4 [96]. In addition, LncRNA NR2F1-AS1 increases breast cancer angiogenesis via stimulating the IGF-1/IGF-1R/ERK pathway [46], which it does by inhibiting miRNA-338-3p. Based on the findings of the aforementioned investigations, miRNA-338-3p is a key tumor suppressor in breast cancer. Furthermore, it has been observed by Duan et al. [97] that the natural substance Baicalin may inhibit breast cancer cell viability, invasion, and induce apoptosis by elevating the expression of miRNA-338-3p.

In Mojdeh Mahmoudian and colleagues’ study, it was discovered that certain microRNAs showed increased expression in BC tumor compared to the adjacent tissues. Specifically, has-miR-25-3p, -29a-5p, -105-3p, and -181b-1-5p were upregulated, while has-miR-335-5p and -339-5p were downregulated. The upregulation or downregulation of these candidate microRNAs was found to be associated with TNM stages, except for has-miR-339-5p. Additionally, with the exception of has-miR-105-3p, each candidate microRNA correlated with HER-2 status. Furthermore, the analysis of ROC curves revealed that the combination of these six microRNAs could potentially serve as a biomarker to differentiate between tumor and non-tumor breast tissue samples.
3.7. ovarian cancer

Another prevalent malignancy in women is ovarian cancer. The expression of miRNA-338-3p was shown to be lower in cisplatin-resistant ovarian cancer tissues, as reported by Niu et al. Overexpression of this gene has been shown to increase sensitivity to cisplatin, trigger apoptosis, suppress cell proliferation, and reverse the EMT process [98]. Reduced lactate generation and cell proliferation are the results of miRNA-338-3p's suppression of PKM2 expression [99]. In addition, miRNA-338-3p repressed EMT by reducing MACC1 expression and blocking the Wnt/beta-catenin and MEK/ERK signaling pathway [100]. Repressed miRNA-338-3p expression was also shown to be inversely linked with poor prognosis in epithelial ovarian cancer [101]. Furthermore, miRNA-338-3p inhibited tumor development in patients with ovarian epithelial carcinoma by targeting Runx2 [102]. In addition, Liu demonstrated that LINC00460 stimulated miRNA-338-3p sponging to induce carcinogenesis in epithelial ovarian cancer [33]. MiRNA-338-3p was shown to be a tumor suppressor in ovarian cancer, as evidenced by the research presented above.

3.8. Cancer of the prostate and microRNA-338

Prostate cancer (PCa) is the leading malignant tumor diagnosed among men. Although miRNA-338-3p levels were shown to be lower in prostate cancer tissues, its overexpression inhibited tumor growth, invasion, and metastasis via reducing RAB23 expression [103]. Additionally, RAB25, another RAS oncogene family member, may be inhibited by miRNA-338-3p [45]. Moreover, Bakkar et al. [104] showed that miRNA-338-3p may negatively affect the CXCR axis and limit proliferation and migration in PCA patients’ cancer specimens compared with nearby benign prostate tissue. Additionally, IncRNA SNHG15 may act as a sponge for miRNA-338-3p, which has been shown to have a tumor-suppressing effect in prostate cancer by targeting FKBP1A [26]. The expression of miRNA-338-3p is suppressed by circHIPK3, which is a direct target of circHIPK3 [56, 105]. Additionally, miRNA-338-5p methylation was shown to be elevated in SPINK1-positive prostate cancer compared to matched noncancerous tissues. It has been shown that miRNA-338-5p, when expressed exogenously, may inhibit tumor stemness, treatment resistance, tumor burden, and tumor metastasis [22]. Both miRNA-338-3p and miRNA-338-5p were shown to be tumor suppressors in the prostate cancer study.

3.9. Glioma and microRNA-338

Invasiveness is a major problem with gliomas, which are prevalent malignant tumors of the central nervous system. MiRNA-338-5p, which is known to inhibit cell proliferation and invasion [106], was shown to be considerably downregulated in glioma. The MAPK-signaling pathway was blocked by overexpressing miRNA-338-5p, which in turn sped up senescence and apoptosis. MiRNA-338-5p inhibited proliferation, migration, and invasion in glioblastoma, and induced apoptosis by directly targeting EFEMP1 [108]. Additionally, chidamide, a small molecule drug, may increase production of miRNA-338-5p, which then inhibits cell growth and invasion by downregulating the Hedgehog signaling pathway [109].

Heavier histological grade was shown to be associated with lower miRNA-338-3p expression in glioma tissues [110]. Reducing OXSM expression with miRNA-338-3p inhibits glioblastoma cell growth [111, 112. In addition, Yu et al. demonstrated that miRNA-388-3p decreased cell survival, migration, and tube formation by downregulating EGFL7 expression [36]. Increased SMO expression and glioma development were also facilitated by CircRNA-SMO's sponging of miRNA-338-3p [27]. LINC00689 facilitated the expression of PKM2 and the development of gliomas by interacting with miRNA-338-3p [34]. Overexpression of miRNA-338-5p dramatically reduced proliferation and produced cell cycle arrest, but not miRNA-338-3p [113], as was also reported in a work by Besse. Based on these data, we propose that miRNA-338 up-regulation as an approach for glioma therapy since it may function as a tumor suppressor in this disease. On the other hand, miRNA-338-5p has been shown to increase glioma cell invasion via controlling TSHZ3 and MMP2 [114], suggesting that it may act as an oncogene. Therefore, further research is required to determine miRNA-338's function in glioblastoma.
3.10. MiR-338 and Related Malignancies

In osteosarcoma, miRNA-338-3p may downregulated RUNX2 and CDK4, respectively, to prevent the tumor development and spread via MAPK pathway suppression [115]. In addition, miRNA-338-3p's targeting of AHSA1 may reduce the proliferation and EMT of osteosarcoma cells [116]. MiRNA-338-3p expression was inversely linked with TNM stage and lymph node metastases in renal cell carcinoma (RCC) and was dramatically downregulated in this disease [117]. Additionally, miRNA-338-3p may target AKT to decrease RCC development [118] and ALK5 to prevent invasion [119]. Furthermore, miRNA-338-3p was shown to inhibit the development of thyroid cancer by targeting the protein AKT3 [120]. MiR-338-3p was shown to be downregulated in melanoma and to target MACC1 to suppress cell proliferation, migration, and invasion [12]. Zhang et al. [121] demonstrated that miRNA-338-3p inhibits bladder cancer cell growth, metastasis, and EMT via targeting EST1. Further evidence that miRNA-338-3p inhibits ccRCC development by downregulation of ETS1 expression was identified in a study by Yang et al. [50]. Using a direct target of HIF-1, miRNA-338-3p suppressed the ERK signaling pathway and cisplatin resistance in nasopharyngeal cancer [122]. Numerous cancer types, including oral squamous cell carcinoma [37], colon cancer [61], and multiple myeloma [58], [123], have been linked to miRNA-338-3p's tumor-suppressing properties. Although these investigations supported the idea that miRNA-338 served as a tumor suppressor, contrary findings persisted. Overexpression of miRNA-338-5p, for instance, has been linked to melanoma and may promote metastasis [124]. In addition, miRNA-338-5p may downregulated RUNX2 and CDK4, respectively, to prevent the tumor development and spread via MAPK pathway suppression [115]. In addition, miRNA-338-3p was shown to inhibit the development of thyroid cancer by targeting the protein AKT3 [120]. MiR-338-3p was shown to be downregulated in melanoma and to target MACC1 to suppress cell proliferation, migration, and invasion [12]. Zhang et al. [121] demonstrated that miRNA-338-3p inhibits bladder cancer cell growth, metastasis, and EMT via targeting EST1. Further evidence that miRNA-338-3p inhibits ccRCC development by downregulation of ETS1 expression was identified in a study by Yang et al. [50]. Using a direct target of HIF-1, miRNA-338-3p suppressed the ERK signaling pathway and cisplatin resistance in nasopharyngeal cancer [122]. Numerous cancer types, including oral squamous cell carcinoma [37], colon cancer [61], and multiple myeloma [58], [123], have been linked to miRNA-338-3p's tumor-suppressing properties. Although these investigations supported the idea that miRNA-338 served as a tumor suppressor, contrary findings persisted. Overexpression of miRNA-338-5p, for instance, has been linked to melanoma and may promote metastasis [124]. In addition, miRNA-338-5p plays an oncogenic function in the advancement of retinoblastoma [125], and its expression is enhanced in this cancer. In Table 3, we compile data on miRNA-338 expression, miRNA-338 subtypes, miRNA-338 target tissues, and miRNA-338 functions in different human malignancies.

4. Biomarker for diagnosis and prognosis: microRNA-338

During the process of carcinogenesis, cancer commonly progressed from an early to a later stage. Therefore, early tumor detection is vital for the cancer treatment. Several lines of evidence point to the potential function of miRNAs as diagnostic or prognostic biomarker, including differential expression of certain miRNAs in tumor tissues and the ability of miRNAs to persist in the blood of patients with cancer. The upregulation of miRNA-338 expression in the blood of individuals with postmenopausal osteoporosis suggested that this may be a diagnostic concern [16]. In addition, individuals with knee osteoarthritis had substantially higher blood miRNA-338-3p levels, suggesting its potential as a new biomarker for the diagnosis of KOA [126]. Furthermore, recent research has shown that miRNA-338 may be exploited for the diagnosis and prognosis of cancer due to its abnormal expression in a variety of malignancies.

Bioinformatics investigation suggested that miRNA-338-5p might be displayed positive utility in detecting hepatocellular carcinoma [127] and a possible prognostic biomarkers in NSCL [128]. While doing so, Han and coworkers discovered a potential new noninvasive prognostic and predictive biomarker for ESCC: miRNA-338-5p downregulation in blood samples [95]. Furthermore, miRNA-338-3p may be an independent prognostic factor for GC since its downregulation in GC was favorably related with aggressive clinical features [83]. Furthermore, it has been observed that in epithelial ovarian cancer, reduced expression of miRNA-338-3p is related to a higher FIGO stage, a higher histological grade, and the presence of lymph node metastases [101]. These findings suggested that miRNA-338 might serve as a diagnostic or predictive biomarker for cancer.

5. Perspectives and Final Thoughts

Since their discovery, miRNAs have been found to influence almost all cellular pathways involved in the beginning and progression of human malignancies. MiRNA-338 is a member of the miRNA family that has been shown to be down-regulated in several types of cancer. MicroRNA-338 (miRNA-338) functions as a tumor suppressor by blocking several oncogenic signaling pathways. Inhibiting IRS2 expression is one mechanism by which miRNA-338-3p controls the insulin signaling pathway and thereby inhibits tumor growth [68]. As may be seen in Fig. One, miR-338 may control the signaling pathways of Wnt–catenin, insulin, Hedgehog, and mitogen-activated protein kinases (MAPKs). Notably,
the function of miRNA-338 may be blocked by ceRNA mechanism. In Fig. 1, we depicted the connection between lncRNAs and circRNAs, two components of the ceRNA process. Summary of the lncRNA-miRNA-338 and circRNA-miRNA-338 networks are shown in Tables 1 and 2, respectively.

Given miRNA-338’s essential role in controlling cell proliferation, apoptosis, migration, and invasion, they may have a significant effect on the responsiveness to chemotherapy and radiation. Overexpression of miRNA-338-3p would sensitize HCC cells to sorafenib [80], and it has been observed that it is typically downregulated in HCC clinical samples. Targeting ABCB1, which may make HCC cells more sensitive to doxorubicin and vinblastine, is the job of miRNA-338-5p [81]. Additionally, induced expression of miRNA-338-5p may restore sensitivity to the chemotherapeutic agent 5-fluorouracil (5-FU) in esophageal squamous cell carcinoma (ESCC) [95]. MiRNA-338-5p inhibits cisplatin resistance in ESCC by targeting FERMT2 [94], suggesting that it has an anti-oncogenic effect in this disease. MiRNA-338-5p increases the susceptibility of ESCC to chemotherapy, as well as the sensitivity to radiotherapy, and induces cell death [93]. Cell sensitivity to cisplatin may be improved by overexpressing miRNA-338-3p, which was shown to be downregulated in cisplatin-resistant ovarian cancer tissues.

Iodine-125 irradiation has been shown to upregulate miRNA-338 expression and inhibit carcinogenesis [129], which is an intriguing finding. Duan et al. proven that natural anti-cancer drug, Baicalin, may boost the expression of miRNA-338-3p and suppress breast cancer carcinogenesis [97]. Chidamide also inhibits the proliferation, migration, and invasion of human malignant glioma cells by inducing overexpression of miRNA-338-5p [109]. Resveratrol therapy has also been shown to increase miRNA-338-3p [130]. Collectively, our results suggested that miRNA-338 may represent a promising therapeutic avenue for treating human cancer. Despite its role as a tumor suppressor, several studies have shown that miRNA-338 may also promote tumor growth, miRNA-338-3p may enhance the development of acute myeloid leukemia [13]. MiRNA-338-5p promoted colon cancer cell migration, invasion, and metastasis [91, 92]. It has been observed that miRNA-338-5p promotes melanoma cell proliferation and metastasis [124]. Cell proliferation was boosted in osteosarcoma, while apoptosis was inhibited, thanks to miRNA-338-5p [65]. These findings suggest that miRNA-338’s role may vary between tumor types. Therefore, future studies should concentrate on elucidating the unique roles of each miRNA-338 expression type, 3p or 5p, in relation to various cancers.

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