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MiR-144: a new possible therapeutic target in cancers

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Abstract

MicroRNAs (miRNAs) are small and non-coding RNAs displaying aberrant expression in the tissue and plasma of cancer patients in comparison to healthy individuals. In past decades, accumulating data proposed that miRNAs could be diagnostic and prognostic biomarkers in cancer patients. It has been identified that miRNAs can act either as oncogenes through silencing of tumor inhibitors or tumor suppressor via targeting oncoproteins. MiR-144 is located in chromosomal region 17q11.2 that was widely destroyed in many types of cancers. Several studies revealed that miR-144 has different target genes including rapamycin, zonula occludens1, SFRP1, and ANO1. MiR-144 acts as a tumor suppressor or oncogene by targeting specific genes. In this review, we define the role of miR-144 and its targets in different cancers and provide understanding in tumor proliferation, migration, and apoptosis.

Keywords: Cancer, microRNA, miR-144, Therapeutic target

Abbreviations

miRNAs: MicroRNAs, 3'-UTR: 3'-untranslated region, GTP: guanosine triphosphate, GDP: guanosine diphosphate, Exp5: Exportin5, RISC: RNA-induced silencing complex, EMT: epithelial-to-mesenchymal transition, PBX3: pre-leukemia transcription factor 3, GC: Gastric cancer, COX-2: Cyclooxygenase-2, CRC: Colorectal cancer, ANO1: Anoctamin 1, EGFR: epidermal growth factor receptor, CXCL11: C-X C motif chemokine ligand 11, *mTOR:* mammalian target of rapamycin, PC: Pancreatic cancer, HCC: Hepatocellular carcinoma, Nrf2: The nuclear factor erythroid 2–related factor 2, E2F3: E2F transcription factor 3, EVs: extracellular vehicles, TUG1: taurine upregulated gene 1, EC: Esophageal cancer, CDDP: cisplatin, Lhx2: LIM homeobox 2, OC: ovarian cancer, KIF14: kinesin family member 14, PrC: Prostate cancer, RCC: Renal cell carcinoma, ARID1A: AT-rich interactive domain-containing protein 1A, BlC: Bladder cancer, EZH2: enhancer of zeste homolog 2, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, NCS1: neuronal calcium sensor 1, SLC44A5: solute carrier family 44 member 5, MARCKS: myristoylated alanine rich protein kinase C substrate, HOXA10: Homeobox A10, GLUT1: glucose transporter 1, ATF2: activating transcription factor 2, ZEB1 and ZEB2: zinc finger E-box-binding homeobox 1 and 2, HNSCC: Head and neck squamous cell carcinoma, IRS1: insulin receptor substrate 1, PTEN: phosphatase and tensin homolog, NPC: Nasopharyngeal carcinoma, TC: Thyroid cancer, WWTR1: WW domain-containing transcription regulator protein 1, GBM: Glioblastoma, c-MET: tyrosine-protein kinase Met, TOP2A: topoisomerase II alpha, FZD7: Frizzled-7, TIGAR: TP53-induced glycolysis and apoptosis regulator, IDH: isocitrate dehydrogenase, OS: Osteosarcomas.

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Introduction

MicroRNAs (miRNAs) are small (20–23 nucleotides) noncoding RNAs that conserved evolutionarily [1]. Today, over than 28,000 identified mature miRNAs do not encode proteins but they can regulate gene expression of approximately 30% of biological proteins [2]. These epigenetic molecules regulate the expression of various genes involved in critical physiological processes including differentiation, proliferation, and apoptosis by binding to 3'-untranslated region (3'-UTR) of a mRNA molecule [3]. MiRNAs indicate a new perspective in the study of cancers. More than 50% of miRNA genes were discovered to be located within genomic regions involved in cancers, suggesting their role in human cancer pathogenesis (16, 17). In pathological condition, MiRNAs can regulate gene expression negatively and are associated with tumor growth, apoptosis, invasion, and metastasis. In the past decades, several studies have pointed the ability of miRNAs in inhibition of tumors as a critical option for improvement of cancer therapy [4, 5]. Tumor activator miRNAs, called oncomiRs are overexpressed in various cancers, on the contrary suppressive tumors miRNAs are underexpressed [6-8]. Among several miRNAs evaluated, miR-144 resemble to have an intrigue role in several cancer. This miRNA is located in chromosomal region 17q11.2 that was widely destroyed in many types of cancers. The predicted stem-loop structure of miR-144 recognized by the miRBase (http://mirbase.org/) is shown in **Figure 1A**. The miR-144 hairpin gives rise to the “guide strand” miR-144-5p and the sister “passenger” strand miR-144-3p **(Figure 1B)**.

Several studies revealed that miR-144 has different target genes including rapamycin, zonula occludens1, SFRP1, and ANO1. MiR-144 by targeting specific genes acts as a tumor suppressor or oncogene. However, previous studies have demonstrated that miR-144 is significantly dysregulated in cancers, even if up-regulation or down-regulation of it in tumors are not yet clarified (**Figure 2**) (18). In this review, we will determine the role of miR-144 and its targets in different cancers and provide understanding into how this miRNA mediates proliferation, migration, and apoptosis in tumors.

Biogenesis of miRNAs

Initially, miRNAs are transcripted by RNA polymerase II as long primary-miRNA (pri-miRNA) transcripts in the nucleus. A nuclear RNase III Drosha (pri-miRNAs) with the cofactor DGCR8 forming the microprocessor complex, which cleaves primary miRNAs at the base of the hairpin and makes a hairpin structured precursor (pre-miRNA) [9]. The pre-miRNA, which has a 2-nt 3′ overhang, because of Drosha's RNase III activity, is exported to the cytoplasm by Exportin5 (Exp5), a RanGTP-dependent double strand RNA-binding protein [10]. Afterward, Exp5 liberates pre-miRNA by hydrolyzing guanosine triphosphate (GTP) to guanosine diphosphate (GDP). Then, pre-miRNA is cleaved by Dicer, another RNase, to create a duplex of miRNA with an average of ~22 base pairs (bps) with a 5 prime (_5p) and a 3 prime (_3p) strand [11]. Due to the relevant thermodynamic stability of the two ends, one of the strands will be maintained [12]. Dicer-binding proteins and other RNAs including PACT and TRBP can simplify miRNA duplexes production and transfer of mature miRNAs to Ago proteins [13] (**Figure 3)**. In the case, the miR-144-3p arm of this miRNA exhibits functionally relevant and the most abundant arm of it [14]. Following to its link with RNA-induced silencing complex (RISC), miRNAs act by a 6-8-mer sequence, a seed sequence, binding to the 3′ UTR of mRNA transcripts complementarily by canonical Watson-Crick base pairing to control target expression [15].

MiR-144 in Gastrointestinal Cancers

MiR-144 in gastric cancer

Gastric cancer (GC) is the second most prevalent cause of cancer-related mortalities worldwide with nearly 740000 deaths annually [16]. Based on evidences, miR-144 has several targets in gastric cancer including ZFX, FOSB, SUCLA2, LSM14A, and HDHD2[17]. Akiyoshi S et al. found that down-regulation of MiR-144 leads ZFX upregulation and is associated with GC progression [18]. MiR-144 reduces GC development by downregulation of MET signaling, which eventually blocks activation of Akt pathway [19]. Moreover, miR-144 has an important role in inhibition of epithelial-to-mesenchymal transition (EMT) and decreased F-actin expression in tumor cells through targeting pre-leukemia transcription factor 3 (PBX3) in GC cells [20]. MiR-144 significantly inhibited proliferation, migration, and invasion in GC cells. Cyclooxygenase-2 (COX-2), PIM1 and GSPT1 are other known targets of miR-144 suggesting the role of miR-144 as a tumor suppressor in gastric cancer [21-23].

MiR-144 in colorectal cancer

Colorectal cancer (CRC) represents the third malignancy for cancer incidence. Metastases are the main cause of mortality in CRC patients. Several studies improve the knowledge of molecular mechanisms of CRC mediatization, even if, these are still not well understood [24]. Mir-144 could be one epigenetic regulator of mediatization, since Anoctamin 1 (ANO1), a miR-144 target gene located on chromosome 11q13, is involved in various biological processes, including angiogenesis, chemotaxis, and adherence. Moreover, downregulation of miR-144, through targeting of ANO1, leads to the activation of the epidermal growth factor receptor (EGFR) or MAP kinase signaling pathways, two of the main involved driver pathway in CRC [25]. C-X C motif chemokine ligand 11 (CXCL11) is another target of miR-144 in CRC. CXCL11 was significantly upregulated in CRC tissues, while miR-144 was downregulated. Upregulation of miR-144 via downregulation of CXCL11 lead to inhibition of inflammation and tumorigenesis [26]. The mammalian target of rapamycin (*mTOR*) a serine/threonine protein kinase, involved in several biological processes such as cellular growth, metabolism, and the cytoskeleton regulation resembles to be is another target of miR-144 [27]. Recent studies showed that the down-regulation of miR-144 leads to mTOR activation and cancer development [28].

Other studies demonstrated that miR-144 is overexpressed in feces of CRC patients and can be used for CRC screening [29, 30]. In a randomized trial, Choi HH et al. investigated the expression of miR-92a and miR-144 as noninvasive biomarkers in stool samples of CRC patients. In this study stool samples were collected from 29 patients with CRC and 29 healthy controls, and the expression of miR-144 with other miRNAs including miR-21, miR-92a, and miR-200c were measured by Real-time PCR. Eventually, the result showed the mean levels and the sensitivity of miR-144 differed significantly between the CRC group and the control group ($p < 0.001$, sensitivity 89.7%) and miR-144 may be an useful marker for detection of CRC [31]

MiR-144 in pancreatic cancer

Pancreatic cancer (PC) is still now one of the more aggressive cancer with a 5-year survival of less than 5% [32]. Several miRNAs could be predictive/prognostic biomarkers and/or therapeutic targets in PC [33].

In an in vitro/ex vivo study, Li J et al. demonstrated that miR-144-3p was reduced in PC tissues and PANC-1 cells [34]. MiR-144-3p expression inhibits cell growth in the S-phase cell-cycle, leading to cell apoptosis in vitro. MiR-144-3p regulated proline-rich protein 11 (PRR11 3'-UTR). When PC cells were transfected with miR-144-3p, PRR11 resulted inhibit, with upregulation of p-JNK and p-p38, with a key role in cancer progression impairment. On the contrary, PRR11 activation reduced miR-144-3p induced apoptosis and cycle arrest in vitro. So far, miR-144-3p induced cell cycle inhibition and apoptosis in PC cell impairing PRR11. Also in another in vitro study, MiR-144-3p results downregulated in vitro evaluations. MiR-144-3p overexpression reduces PC cell growth, chemotaxis, and metastasis [35]. Liu S et al. demonstrated that MiR-144-3p enhancing could downregulated PC cell migration, proliferation, and invasion by inhibiting the expression of FOSB

So far, enhancing miR-144 could provide a new target against PC, even if more studies are warranted.

MiR-144 in hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the ninth major cause of cancer deaths in the United States and the most common form of primary liver malignancy [36]. In the liver tumors, miR-144 was significantly reduced compared to non-tumor tissues. MiR-144 leads to knock down of EGFR/Src/AKT axis by targeting EGFR in mice HCC. Decreased levels of miR-144 are correlated with increasing in growth and metastasis of HCC cells [37]. The nuclear factor erythroid 2–related factor 2 (Nrf2) is a resistance regulator of oxidants in cells [38]. MiR-144 triggers Nrf2 mRNA degeneration by targeting the 3'UTR region and leads to reverse chemoresistance in HCC cell lines [39]. E2F transcription factor 3 (E2F3) belongs to the E2F family and has two isoforms, E2F3a and E2F3b [40]. Cao et al. displayed that miR-144 suppresses HCC proliferation and metastasis by targeting E2F3 [41]. Another study detected that the levels of miR-141-3p were significantly increased in serum extracellular vehicles (EVs) and liver cancer tissues compared with serum and the distal liver tissues in HCC patients [42]. MiR-141-3p also leads to invasion and metastasis of HCC by direct targeting of SMAD4 and SGK3 [43, 44]. Yu M et al. assessed the role of miR-144 in HCC. They found that the expression of miR-144 was regularly downregulated in human HCC tissues and cell lines, and overexpression of miR-144 via direct targeting of SMAD4, significantly repressed metastasis, invasion, cell

cycle, EMT, and resistance to chemotherapy [45]. Lu et al. proposed that upregulation of miR-144 through direct targeting of taurine upregulated gene 1 (TUG1) contributed to inactivation of the JAK2/STAT3 pathway impairing proliferation, migration, and tumorigenesis in HCC [46].

MiR-144 in esophageal cancer

Esophageal cancer (EC) is a common cancer of digestive system which affects more than of 450000 people in the world [47]. Previous studies exhibited that the down-regulation of miR-144/451 is related to the higher risk of EC [48]. High expression of miR-144-3p, miR-144-5p, and miR-451 through targeting Myc and P-ERK led to apoptosis and inhibition of migration, invasion, and proliferation of EC cells [49]. Another study by Sharma P et al. revealed that miR-144 is an oncomiR in EC cells by targeting PURA [50]. They examined the role of miR-144 in EC by silencing it in KYSE-410 cells, and followed this with cell cycle analysis and the cell viability and invasion assays such as MTT, annexin, and matrigel invasion assay. Their result showed the miR-144 blocked significantly suppressed EC cell proliferation at 72 hours post-transfection ($p=0.029$). Also, the inhibition of miR-144 dramatically reduced the migration, and invasion of KYSE-410 cells compared to cells treated with negative control (NC). Also, overexpression of miR-144 in serum samples of EC patients indicates its role as non-invasive prognostic biomarker [51].

MiR-144 in genitourinary system

MiR-144 in cervical cancer

Cervical cancer is the most common gynecological malignancy and the eighth most common cancer in the world [52]. MiR-144 is significantly decreased in cervical cancer cells compared to normal cervical cells. MiR-144 suppresses proliferation and angiogenesis by targeting VEGFA and VEGFC in cervical cancer cell [53]. Furthermore, miR-144 overcomes resistance to cisplatin (CDDP) through targeting of LIM homeobox 2 (Lhx2), leading to apoptosis and inhibiting invasion in cervical cancer cells [54]. Also, Wu et al. displayed that miR-144-3p inhibited the growth and metastasis of cervical cancer cells, by targeting mitogen-activated protein kinase 6 (MAPK6) [55]. These results showed miR-144 also can act as new clinical targets for the management of cervical cancer.

MiR-144 in ovarian cancer

Ovarian cancer (OC) is one of the most frequently diagnosed malignant diseases of the women worldwide and causes more than 150,000 women death a year [56]. The expression of miR-144, miR-93, and miR-382 were reduced in primary ovarian tumors. Down-regulation of miR-144 by targeting the oncogene kinesin family member 14 (KIF14), led to transcriptional and epigenetic regulation [57]. Moreover, downregulation of miR-144 and miR-216 have a critical role in lymphovascular invasion of ovarian cancer [58]. Some studies suggested that therapeutic potential of miRNAs targeting in the regulation of EMT and apoptosis could contribute to the higher risk of ovarian cancer [59, 60].

MiR-144 in prostate cancer

Prostate cancer (PrC) is one of the most common cancer among men and the third major cause of cancer death in men [61, 62]. However early diagnosis of PC through Prostate-Specific Antigen (PSA) testing remains unproven, using other biomarkers have the beneficial to reduce the overdiagnosis related to the PSA screening [63]. Screening of miRNAs, as a new detection way, has revealed controversial results in PrC detecting, but most of them reported upregulation of miRNAs [64]. Liu F et al. reported that overexpression of miR-144 by Beclin-1, an autophagy-associated protein 6, down-regulation, led to increase in tumor cell death [65]. Moreover, they found CDDP treatment may induce VEGF through miR-144 levels suppression in PrC cells, with cell autophagy inhibition. Another study by Gu H et al. found that miR-124 and miR-144 directly target the 3′UTR of PIM1 and via its downregulation, led to hypoxia-induced autophagy and increase radiosensitivity of PrC [66]. Zheng H et al. determined that miR-144-3 prevents proliferation and leads to cell death in PrC by targeting CEP55 [67]. Overall, these results suggested that miR-144 could be a novel therapeutic target for PC therapy.

MiR-144 in renal cell carcinoma

Renal cell carcinoma (RCC) accounts for 70-80% of malignancies in the kidney and is the most lethal neoplasm of the urologic system [68]. The role of miR-144 in embryonic alpha-hemoglobin synthesis and erythroid homeostasis has been recognized in previous studies. Xiang C et al. found overexpression of miR-144 via targeting mTOR, inhibits proliferation and S/G2

cell cycle arrest in tumor cells [69]. Furthermore, miR-144-3p lead to suppression of invasion and migration, by targeting MAP3K8, so far, it can act as a tumor suppressor [70].

Overexpression of miR-144-3p leads to proliferation, metastasis and Sunitinib resistance by targeting AT-rich interactive domain-containing protein 1A (ARID1A) in clear cell RCC [71]. Also in a recent survey, the antitumor roles of miR-451a, miR-144-5p, and miR-144-3p were confirmed in RCC [72]. Assays determined that miR-144-5p and miR-144-3p significantly reduced migration and invasion in RCC cells, proposing these miRNAs behaved as tumor suppressor miRNAs in RCC. Computational analyses recognized a total of 65 possible targets of miR-144-5p in RCC cells. Among them, high expression of FAM64A, F2, TRIP13, ANKRD36, CENPF, NCAPG, CLEC2D, SDC3, and SEMA4B were dramatically connected with poor prognosis ($P < .001$). Among them, the expression of SDC3 was directly regulated by miR-144-5p, and its upregulation enhanced RCC cell invasiveness.

MiR-144 in Bladder cancer

Bladder cancer (BlC) is one of the highly prevalent cancers and causes 16,000 deaths annually in USA. Carcinogens including environmental and occupational exposures are the main cause of bladder cancer [73]. The role of miRNAs in BlC has been investigated in several studies. Guo Y et al. demonstrated that high expression of miR-144 by targeting enhancer of zeste homolog 2 (EZH2) leads to regulation of Wnt pathway and inhibits proliferation of tumor cells. Therefore, miR-144 acts as a tumor suppressor in bladder cancer [74]. Matsushita R et al. found miR-144-5p acts as tumor suppressor by directly targeting CCNE1/2 in in bladder cancer [75]. This study was conducted to evaluate the functional roles of miR-144-3p and miR-144-5p and their modulation of targets in BlC cells. Their results showed that miR-144-5p via direct targeting of CCNE1, CCNE2, CDC25A, and PKMYT1 dramatically repressed cell proliferation of BlC cells. Also, patients with higher expression of CCNE1 or CCNE2 had lower overall survival rates than those with low expression ($P=0.025$ and $P=0.032$). Thus, the current results proposed that overexpression of miR-144 can act as a new clinical target in BC therapy.

MiR-144 in lung cancer

Lung cancer including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) is a leading cause of cancer-related deaths worldwide for both males and females [76]. The role of

miR-144 in lung cancer was assessed in several studies. The concentrations of miR-144 duplex (miR-144-5p and miR-144-3p) were significantly reduced in squamous NSCLC tissues compared to healthy adjacent tissues. It was observed that both miR-144-5p and miR-144-3p had tumor inhibitory effects by targeting several oncogenes in squamous NSCLC including neuronal calcium sensor 1 (NCS1), solute carrier family 44 member 5 (SLC44A5), and myristoylated alanine rich protein kinase C substrate (MARCKS) genes [77]. Upregulation of miR-144 enhance LINC00483 and Homeobox A10 (HOXA10) genes in lung adenocarcinoma resulting in a tumor suppressor activity through regulation of EMT [78]. Chen et al. indicated that miR-144 negatively controls TIGAR expression and induces apoptosis and autophagy in Lung Cancer [79]. MiR-144 is detected in lung cancer cells with expression of upregulated glucose transporter 1 (GLUT1) and enhanced glucose uptake [80]. Moreover, miR144 increases the radiosensitivity in NSCLC cells by targeting activating transcription factor 2 (ATF2) [81]. These results suggest that regulation of miR-144 could represent a potential clinical target in lung cancer.

MiR-144 in breast cancer

MiR-144 via several targets acts as a tumor suppressor in breast cancer. Pan Y et al. showed MiR-144 can target a 3′-UTR of zinc finger E-box-binding homeobox 1 and 2 (ZEB1 and ZEB2) and control their expression at transcriptional and translational levels. Also, this study showed that the expression of miR-144 can repress the process of EMT in MCF-7 and MDA-MB-231 cell lines [82]. Also, miR-144 via downregulation of CEP55 could inhibit proliferation, invasion, and migration, retarding cell cycle and accelerating apoptosis of breast cancer cells [83]. Another study by Yu L et al. found that miR-144 may act as an oncomiR by an increase in the survival rate of breast cancer cells. Overexpression of miR-144 increased the proliferation rate of tumor cells in the MDA-MB-231 cell line. Also, the migration and invasion of tumor cell lines of MDA-MB-231 and SKBR3 were increased by elevated miR-144 expression [84].

MiR-144 in head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) is a member of highly aggressive tumors that involve the epithelium numerous anatomical sections such as the oral cavity [85]. Zhang et al. demonstrated that MiR-144-3p by targeting of ETS-1 and insulin receptor substrate 1 (IRS1) in laryngeal squamous cell carcinoma led to inhibition in metastasis and invasion of tumor cells.

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Moreover, miR-144-3p by inhibition of E-cadherin reduces cellular EMT in laryngeal squamous cell carcinoma [86, 87].

MiR-144 in nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is a type of head and neck cancer emerging from the epithelial cells in the nasopharynx. The NPC incidence is very higher in Southeast Asia and North Africa compared to other region of the world [40]. Downregulation of anti-oncogenes in NPC by miRNAs has been recognized as an important mechanism of tumorigenesis. Zhang et al. concluded that microRNA-144 by downregulation of phosphatase and tensin homolog (PTEN) mediates cell proliferation, invasion, and metastasis in NPC [88]. Also Song et al. demonstrated that miR-144 upregulation was related to PTEN downregulation in NPC [89]. Moreover in an in vitro study, downregulation of miR-144 by triptolide leads to increase in p85α-PTEN complex and cause cell cycle arresting in S-phase in human NPC cells [90].

MiR-144 in thyroid cancer

Thyroid cancer (TC) representing for 1% of all malignancies, but it is the most common malignancy of the endocrine system [91, 92]. Guan H et al. found that the expression of miR-144 is significantly lower in TC tissues compared to normal tissues. Moreover, miR-144 targets ZEB 1 and ZEB2 and inhibits the invasion of tumor cells, suggesting the role of miR-144 as a tumor suppressor in TC [93]. Sun J et al. proposed that up-regulation of miR-144 acts as a useful prognostic and clinical target in TC. In particular, the transcription factor E2F8 (a member of E2F family) led to down-regulation of miR-144 with TC cells proliferation [14]. Sun et al. also confirmed that miR-144 suppress proliferation of tumor cells by targeting WW domain-containing transcription regulator protein 1 (WWTR1) in papillary TC [94]. Another in vitro study displayed that miR-144-3p involved in cell cycle progression and EMT. MiR-144 by targeting Paired box gene 8 (PAX8) caused to the activation of signaling pathways including ERK1/2 and Akt with consequent tumors proliferation [95].

MiR-144 in glioblastoma

Glioblastoma (GBM) is the most frequent and malignant tumor brain associated with extremely poor prognosis [96]. Aberrant miRNAs expressions can be used as a diagnostic and prognostic biomarker for GBM [97]. Recent studies showed the role of miR-144 as a tumor suppressor by

targeting tyrosine-protein kinase Met (c-MET). Down regulation of MiR-144-3p in GBM over non-neoplastic brain tissues was verified in several studies [98]. MiR-144-3p negatively exerts tumor growth and apoptosis in glioma cells by targeting topoisomerase II alpha (TOP2A) [99]. Frizzled-7 (FZD7) has been identified as an oncogene responsible of the cancer cells growth by Wnt signaling activation. Cheng et al .indicated that miR-144-3p inhibits metastasis by targeting FZD7 [100]. In addition some studies demonstrated that upregulation of miR-144 increases the level of Gli1, a protein that mediates the Hedgehog‑Gli pathway in GBM [101]. Moreover, overexpression of miR-144 by targeting of PDK1, TP53-induced glycolysis and apoptosis regulator (TIGAR), and isocitrate dehydrogenase (IDH)1 and IDH2 leads to cell invasion [102].

MiR-144 in Melanoma

Melanoma is the most severe type of skin tumors which is prescribed annually more than 130,000 new cases of this malignancy worldwide [103]. Recent findings showed a key role of miRNAs in the progress of melanoma. Down-regulation of miR-144 through targeting of SMAD1 has a regulatory effect on cell proliferation and metastasis in melanoma [20]. Furthermore, miR-144 suppresses the proliferation and invasion of melanoma cells by regulating of c-Met expression [104].

MiR-144 in osteosarcoma

Osteosarcomas (OS) is a rare malignant tumor of bone that annually presents in nearly 3.5 cases per million people [105]. Different miR-144 expression in osteosarcoma has been reported in several studies. Namløs HM et al. discovered a substantial downregulation of miR-451/miR-144 clusters in OS cell lines [106]. Also, Zhao M et al. found downregulation of miR-144 by targeting of TAGLN led to proliferation and invasion of OS tumor cells [107]. They found that miR-144 has downregulated in OS cell lines and tissue samples and its expression suppressed proliferation and invasion of OS cells. Also, upregulation of TAGLN, as a target of miR-144, is inversely associated with miR-144 expression .ROCK1 and ROCK2 are another targets of miR-144 that downregulation of them by upregulation of miR-144 has an important role in suppressing of proliferation and invasion [108]. MEF2D, Ezrin, and mTOR are other possible targets of miR-144 that inversely upregulated in OS, suggesting the critical role of miR-144 in suppression of tumor growth and metastasis [109-111].

Conclusions

MiR-144 is often down-regulated in multiple cancers and tumor cell lines and plays a significant role in cell proliferation and metastasis. MiR-144 has several important targets including rapamycin, zonula occludens1, SFRP1, and ANO1. MiR-144 by targeting specific genes acts as a tumor suppressor mostly, their expression is controlled by signaling pathways in numerous cancers and playing important roles in the control of cell proliferation, migration, cell death, and tumorigenesis. Reduced expression of miR-144 has been discovered in CRC, GC, OS, and other tumors suggesting the miR-144 as a new therapeutic target in tumor inhibition.

Conflict of interest:

The authors declare that there is no conflict of interest.

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Fig.1.

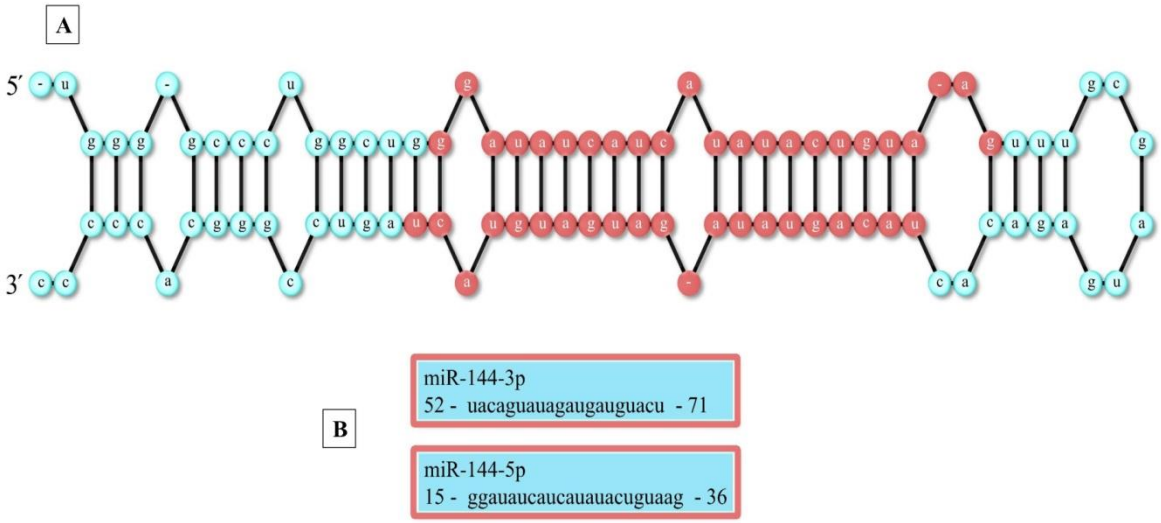

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Fig.2.

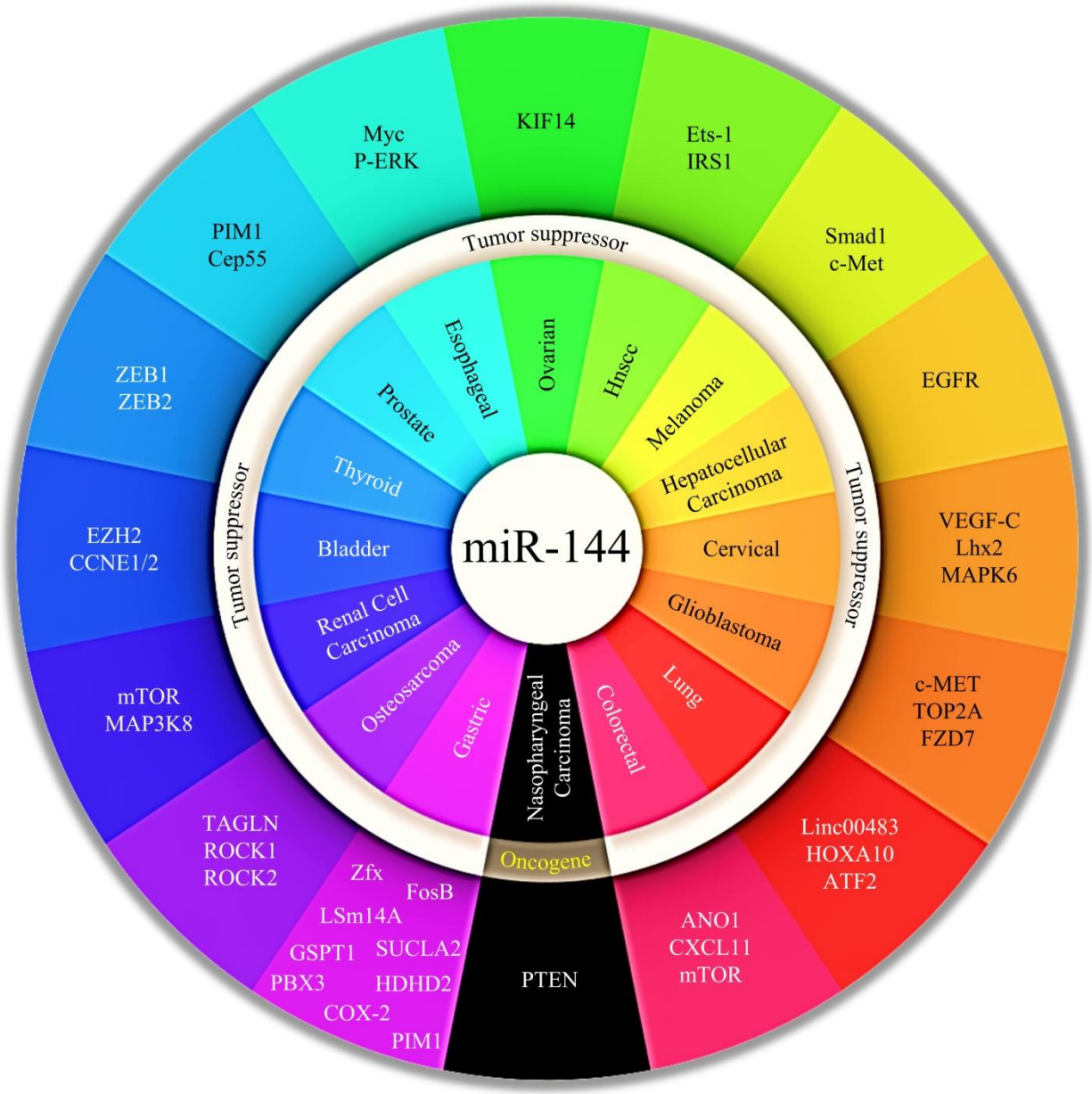

Fig 3.