A review on the role of mir-16-5p in the carcinogenesis

Soudeh Ghafouri-Fard1, Tayyebeh Khoshbakht2, Bashdar Mahmud Hussen3,4, Sara Tharwat Abdullah5, Mohammad Taheri6* and Mohammad Samadian7*

Abstract

miR-16-5p is microRNA with important roles in the development of diverse malignancies including neuroblastoma, osteosarcoma, hepatocellular carcinoma, cervical cancer, breast cancer, brain tumors, gastrointestinal cancers, lung cancer and bladder cancer. This miRNA has 22 nucleotides. hsa-miR-16-5p is produced by MIR16-1 gene. First evidence for its participation in the carcinogenesis has been obtained by studies reporting deletion and/or down-regulation of these miRNAs in chronic lymphocytic leukemia. Subsequent studies have shown down-regulation of miR-16-5p in a variety of cancer cell lines and clinical samples. Besides, tumor suppressor role of miR-16-5p has been verified in animal models of different types of cancers. Studies in these models have shown that over-expression of this miRNA or modulation of expression of IncRNAs that sponge this miRNA can block carcinogenic processes. In the current review, we summarize function of miR-16-5p in the development and progression of different cancers.

Keywords miR-16-5p, Cancer, Biomarker, Expression, Malignancies

Introduction

MicroRNAs (miRNAs) are small-sized transcripts that regulate expression of genes at post-transcriptional level through specific targeting of mRNAs. With sizes about 21–25 nucleotides, miRNAs are originated from coding and non-coding transcription units in introns, exons or intergenic areas [1]. They are produced in a multi-step process involving both nuclear and cytoplasmic proteins. They are involved in the carcinogenic process, since they can regulate expression of several oncogenes and tumor suppressor genes as well as activities of cancer-associated pathways [2]. Expression pattern and function of several miRNAs have been assessed in different cancer types. Since these small-sized transcripts are stable in the circulation or other biofluids, they represent potential biomarkers for diagnostic and follow-up purposes [3]. Dysregulation of miRNAs has been correlated with evolution of cancers, hence they are regarded as molecular...
tools for non-invasive assessment of cancer occurrence and its prognosis [4].

miR-16-5p is an example of this class of transcripts with important roles in the development of diverse malignancies including neuroblastoma, osteosarcoma, hepatocellular carcinoma, cervical cancer, breast cancer, brain tumors, gastrointestinal cancers, lung cancer and bladder cancer. This miRNA has 22 nucleotides and is present in Homo sapiens. Homo sapiens hsa-miR-16-5p is produced by MIR16-1 gene.

miR-16-1 is allocated at 13q14.3 along with miR-15a. This miRNA cluster is the target of 13q deletions in chronic lymphocytic leukemia (CLL). miRNAs encoded by this locus have tumor suppressor functions. First evidence for its participation in the carcinogenesis has been obtained by studies reporting deletion and/or down-regulation of these miRNAs in (CLL) [5]. The tumor suppressor functions of miR-15a/16-1 are exerted through targeting the BCL2 oncogene. Through a high-throughput study in a leukemic cell line model, Colin et al. have found enrichment in AU-rich elements in the elements of the miR-15a/16-1 signature [6].

Subsequently, different studies have assessed role of miR-16-5p in the carcinogenesis using in vitro and in vivo techniques. Moreover, expression pattern of miR-16-5p has been evaluated in clinical samples gathered from patients with diverse malignancies. In the current review, we summarise function of miR-16-5p in the development and progression of different cancers using the above-mentioned lines of evidence. The reason for selection of this miRNA in this review article is the important role of this miRNA in the suppression of carcinogenesis, its down-regulation in a variety of solid and hematological malignancies and its potential as an anticancer target. The following strategy was used for selection of papers: publication in full-text English language in a peer-reviewed journal and detailed description of conducted methods. In addition, papers should include in vitro functional studies or expression assays in clinical samples.

Cell line studies

Cell line studies have indicated important roles of miR-16-5p in the carcinogenesis. Moreover, these studies have shown the inhibitory effects of this miRNA on transcription of several genes, particularly a number of known oncogenes. An in vitro study in neuroblastoma has shown interaction between miR-15a, miR-15b and miR-16 and MYCN transcript. Based on the results of luciferase reporter assay these miRNAs bind with 3'UTR of MYCN transcript leading to suppression of its expression. Forced up-regulation of these miRNAs has decreased proliferative potential, migratory ability, and invasion of neuroblastoma cells [7]. Another study in neuroblastoma has shown that the oncogenic circular RNA circ-CUX1 enhances tumorigenesis of neuroblastoma and their glycolysis through targeting miR-16-5p. Moreover, miR-16-5p tumor suppressor impact has been partially decreased by transfection of circ-CUX1 over-expressing vectors. DMRT2 has been found to be targeted by miR-16-5p in neuroblastoma cells [8].

miR-16-5p has been to be down-regulated in osteosarcoma cell lines compared with control cells, parallel with up-regulation of Smad3. Up-regulation of miR-16-5p has suppressed proliferation, migratory potential and invasive features of osteosarcoma cells and increased the cytotoxic effects of cisplatin on these cells. Moreover, miR-16-5p over-expression has led to reduction of Smad3 expression. Notably, cells harboring Smad3 mutation have not responded to miR-16-5p over-expression, indicating that miR-16-5p suppresses invasive properties of osteosarcoma cells through suppressing expression of Smad3 [9]. miR-16-5p effect in suppression of tetraruspanin 15 gene has also been involved in the inhibition of osteosarcoma cells proliferation, migration and invasion [10]. Figure 1 shows tumor suppressor role of miR-16-5p in different types of cancer.

The long non-coding RNA (lncRNA) AGAP2-AS1 which targets miR-16-5p has been shown to be up-regulated in hepatocellular carcinoma cell lines. This lncRNA could promote proliferation, migratory aptitude, invasiveness and epithelial-mesenchymal transition (EMT) of these cells through acting as a sponge for miR-16-5p. ANXA11 has been found as a target of miR-16-5p in hepatocellular carcinoma cells, mediating the impacts of miR-16-5p and AGAP2-AS1 in these cells and enhancing activity of AKT signaling. Notably, hypoxia has been shown to increase levels of AGAP2-AS1 in these cells [11]. Another study has confirmed down-regulation of miR-16-5p in hepatocellular cancer cells. Dual-Luciferase reporter gene assay has validated the regulatory role of miR-16-5p on expression of Insulin like growth factor1 receptor (IGF1R). IGF1R down-regulation has decreased the suppressive role of miR-16-5p on proliferation ability and metastatic potential of hepatocellular cancer cells [12]. Moreover, down-regulation of miR-16-5p by lncRNA TTN-AS1 has been shown to promote resistance to sorafenib through enhancement of expression of cyclin E1 [13]. Finally, another study in hepatocellular carcinoma has shown that SNHG22 increases tumorigenic ability of cancer cells and their angiogenesis though induction of DNA methylation in miR-16-5p [14].

In cervical cancer cells, miR-16 - 5p affects radiosensitivity through regulation of expression of coactivator - associated arginine methyltransferase 1 [15]. Moreover, it can influence metabolic reprogramming and chemoresistance through regulation of Pyruvate Dehydrogenase Kinase 4 (PDK4) expression [16].
In breast cancer cell, down-regulation of miR-16-5p has been associated with high migratory and proliferative potential of cells, induction of cell cycle progression and reduction of cell apoptosis. miR-16-5p could restrain activity of the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and reduce expression of AKT3 gene, thus inhibiting development of breast cancer [17]. miR-16-5p could also suppress proliferation of breast cancer cells through down-regulating expression of ANLN [18]. The inhibitory effect of miR-16-5p in breast cancer cells proliferation and invasiveness can be mediated through regulation of Vascular Endothelial Growth Factor A (VEGFA) expression [19]. Finally, ATX-N8OS has been shown to enhance tamoxifen resistance through sponging miR-16-5p [20].

Moreover, miR-16-5p has been shown to be commonly down-regulated in astrocytic gliomas. This miRNA could regulate proliferation and apoptosis of these cells as well as effect of cytotoxic agents on these cells [21]. Another study in glioma cells has shown that TIIA could inhibit viability of cells, their migratory potential and invasiveness, and decrease levels of Cyclin
D1, Matrix metallopeptidase 9 (MMP-9) and Vimentin via regulation of miR-16-5p/Talin-1 axis [22].

Summary of studies that evaluated expression of miR-16-5p or its partners in cell lines is presented in Table 1.

Animal studies

The tumor suppressor role of miR-16-5p has been verified in animal models of different types of cancers. Studies in these models have shown that over-expression of this miRNA or modulation of expression of lncRNAs that sponge this miRNA can block carcinogenic processes. For instance, transplantation of miR-15a, miR-15b and miR-16-5p expressing neuroblastoma cells into extremely immunodeficient mice has suppressed formation of tumors as well as expression of MYCN, suggesting that these miRNAs have a tumor suppressor role in neuroblastoma through targeting MYCN [7]. Another study in xenograft model of neuroblastoma has shown that knock down of the miR-16-5p-targeting circ-CUX1 leads to reduction of tumor growth [8]. In animal models of hepatocellular carcinoma, up-regulation of AGAP2-AS1 has enhanced tumor growth via down-regulating miR-16-5p [11]. Moreover, down-regulation of TTN-AS1 decreases tumor size and resistance to sorafenib through enhancement of expression of miR-16-5p [13]. In cervical cancer models, silencing of miR-16-5p target, PDK4 has enhanced efficacy of chemotherapy [16]. Moreover, silencing of DLX6-AS1 which targets miR-16-5p decreases tumor size [25]. Other studies in breast cancer, chordoma/chondrosarcoma, gastric cancer, lung cancer, colorectal cancer, bladder cancer and cholangiocarcinoma have confirmed a tumor suppressor role for miR-16-5p (Table 2).

Human studies

Down-regulation of miR-16-5p has been verified in clinical samples obtained from patients with different malignancies. Moreover, AGAP2-AS1 that decreases miR-16-5p levels has been shown to be up-regulated in hepatocellular carcinoma tissues, particularly in metastatic and recurrent ones. In addition, expression levels of AGAP2-AS1 and miR-16-5p have been correlated with clinical parameters and poor prognosis of patients with this type of cancer [11]. In neuroblastoma, up-regulation in circ-CUX1 that sponges miR-16-5p has been correlated with advanced TNM stage, low differentiation grade and lymph node metastasis [8]. In breast cancer patients, miR-16-5p has been shown to have low expression. Notably, patients with low expression of miR-16-5p have been found to have a lower survival rate compared with those having high expression of miR-16-5p [17].

In the majority of CLL cases, miR-15a and miR-16-1 have been shown to be lost or down-regulated [6]. Moreover, assessment of GO database has led to identification of enrichment of MCL1 Apoptosis Regulator, BCL2 Family Member (MCL1), B-cell lymphoma 2 (BCL2), ETS Proto-Oncogene 1 (ETS1), or Jun Proto-Oncogene, AP-1 Transcription Factor Subunit (JUN) in miR-16 signature. Notably, these genes are involved in the regulation of apoptosis and cell cycle [6].

Several studies have reported down-regulation of this miRNA in nearly all examined malignant tissues except for ovarian cancer tissues. Similarly, lncRNAs or circRNAs that decrease expression of miR-16-5p have been found to be up-regulated in cancer samples compared with non-cancerous controls (Table 3).

Discussion

miR-16-5p is an example of miRNAs with tumor suppressor role in almost all assessed tissues. This speculation is based on the observed down-regulation of this miRNA in nearly all examined malignant tissues except for ovarian cancer tissues. Moreover, a number of studies have reported up-regulation of lncRNAs that target this miRNA or specific targets of this miRNA. This miRNA has been found to be sponged by some lncRNAs and circRNAs, namely LINC00662, LINC00649, LINC00473, LINC00210, PVT1, XIST, AGAP2-AS1, DLX6-AS1, TTN-AS1, circ-CUX1 and hsa_circ_0005721. These observations indicate the complexity of the network through which miR-16-5p exerts its tumor suppressor effects. Moreover, abnormal up-regulation of the mentioned lncRNAs and circRNAs is regarded as a possible mechanism for down-regulation of miR-16-5p along with genomic variations in the genetic locus of this miRNA.

Phosphoinositol 3-kinase (PI3K)/AKT, Phosphatase and tensin homolog (PTEN)/AKT, NF-kB, Hippo and E1-pRB-E2F1 pathways are among signaling pathways being affected by dysregulation of miR-16-5p. Thus, down-regulation of miR-16-5p can lead to over-activity of cancer-related signals enhancing cell survival.

Down-regulation of miR-16-5p or up-regulation of lncRNAs/circRNAs that sponge this miRNA has been shown to be associated with malignant features of different cancers such as neuroblastoma, osteosarcoma, renal cell carcinoma and colorectal cancer, indicating a role for miR-16-5p as a prognostic marker in human cancers. In fact, down-regulation of this miRNA has been detected in samples with low level of differentiation and high propensity to local and distant metastases. Thus, patient with low levels of expression of this miRNA has exhibited poor clinical outcomes.

Since this miRNA can be detected in the peripheral blood, it represents a novel non-invasive strategy for early detection of cancer. However, since it is down-regulated in several types of cancers, the type of cancer cannot be detected through this route. Moreover, evaluation
| Tumor type               | Targets/Regulators and Signaling Pathways | Cell line                                                                 | Function                                                                 | Reference |
|-------------------------|------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------|
| Neuroblastoma           | MYCN                                     | hFOB1.19, MG63, Saos2, HOS, and U2OS                                     | ↑↑ miR-16-5p: proliferation, migration, and invasion                  | [7]       |
|                         | Circ-CUX1, DMR T2                       | HUVEC, GI-LN, SK-N-SH, and IMR-32                                        | ∆ Circ-CUX1 (which suppresses miR-16-5p): proliferation, migration, invasion, and glycolysis | [8]       |
| Osteosarcoma            | Smad3                                    | hFOB1.19, MG63, SaOS2, HOS, and U2OS                                     | ↑↑ miR-16-5p: proliferation, migration, invasion, and ↑ therapeutic effect of cisplatin | [9]       |
|                         | TSPAN15, P13K/ AKT signaling pathway     | hFOB 1.19, MG63, Saos2 and HOS                                           | ↑↑ miR-16-5p: viability, migration, invasion                             | [10]      |
|                         | LINC00662, ITPR1                        | U2OS, SAOS-2, 143B, and MG63, HFOB 1.19                                  | ↓ miR-16-5p: proliferation, migration, invasion, and stemness property maintenance | [23]      |
|                         | hsa_circ_0005721, TET1                  | HFOB, 143B, U-2OS, HOS and Saos-2                                       | ∆ hsa_circ_0005721 (which sponges miR-16-5p): viability, migration, invasion | [24]      |
| Hepatocellular carcinoma| AGAP2-AS1, ANXA11, AKT signaling         | LO2, Hep3B, HCCLM3, Huh7, MHCCK-97 H and SMMC-7721                     | ↑↑ AGAP2-AS1: proliferation, migration, invasion, and ↓ apoptosis       | [11]      |
|                         | IGF1R                                    | SMMC-7721, HL-7702                                                        | ↑↑ miR-16-5p: proliferation, migration, invasion, and EMT process      | [12]      |
|                         | TTN-AS1, cyclin E1, PTEN/Akt signaling   | Bel7404 and HepG2                                                          | ∆ TTN-AS1 (which sponges miR-16-5p): sorafenib resistance, ↑ apoptosis | [13]      |
|                         | SNHG22, EZH2, DNMT1                      | HLE-3, Huh7, HCCLM6, MHCC97H and SNU-398                                 | Δ SNHG22 (which suppresses the transcription of miR-16-5p): proliferation, invasion, and angiogenesis | [14]      |
| Cervical cancer         | CARM1                                    | HeLa, C-33 A, CaSk, HeLa229, SiHa, END1/D667                              | ↑↑ miR-16-5p: ↓ proliferation, glucose consumption, lactate production, and ATP levels, and resistance to Dox treatment | [15]      |
|                         | PDK4                                     | HeLa, SiHa, HeLa/Dox, and SiHa/Dox                                      | ↑↑ miR-16-5p: ↓ proliferation, glucose consumption, lactate production, and ATP levels, and resistance to Dox treatment | [16]      |
|                         | DLX6-AS1, ARPP19                         | End1/E6E7, SiHa, HeLa, C-33 A, and CaSk                                 | ∆ DLX6-AS1 (which sponges miR-16-5p): ↓ proliferation, migration, EMT process, ↑ apoptosis | [17]      |
| Breast cancer           | AKT3, NF-κB pathway                      | BT-549 and MCF-7                                                          | ↑↑ miR-16-5p: ↓ proliferation, migration, ↑ apoptosis, cell cycle arrest | [18]      |
|                         | ANLN                                      | MCF-7, T47D, MDA-MB-231, EMF-192 A, SKBR-3 and MCF-10 A, HEK293T        | ↑↑ miR-16-5p: ↓ proliferation, migration, invasion, and ↑ apoptosis, G2/M phase arrest | [19]      |
|                         | VEGFA, Hypoxia-inducible factor-α (HIF-α) | MCF-7 and MDA-MB-231, MDA-MB-435, MDA-MB-488 and T47D, MCF10A           | ↑↑ miR-16-5p: ↓ proliferation, invasion, colony formation, ↑ apoptosis | [20]      |
|                         | ATXN8OS, VASP                            | MCF-10 A MCF-7, and BT-549                                                | Δ ATXN8OS (which sponges miR-16-5p): tamoxifen sensitivity             | [21]      |
| Gliomas                 | WEE1, CHEK1 and MCL1                     | A172, T98G, U251MG, U381MG and U87 MG, TP365MG                          | ↑↑ miR-16-5p: ↓ proliferation, viability, ↑ apoptosis, cell cycle arrest, response to irradiation and chemotherapy | [22]      |
|                         | TLN1                                      | T98G and A172                                                             | TLE treatment: ↑ miR-16-5p                                             | [23]      |
| Neuroendocrine tumors   | SSTR2                                    | INS-1 rat insulinoma cell line and GH3 rat pituitary GH- and PRL-producing cell line | ↑↑ miR-16-5p: ↓ proliferation, migration, invasion                      | [24]      |
of levels of miR-16-5p in cancer patients can be used for follow-up after removal of primary tumor. The mechanism behind down-regulation of miR-16-5p in malignant tissues is not investigated thoroughly, although deletion in the genomic region coding this miRNA is a putative mechanism. Moreover, up-regulation of lncRNAs/circRNAs that sponge this miRNA is a well-established mechanism for its down-regulation in malignant tissues. In this manner, we can see that miR-16-5p is an interesting target for further investigation as a diagnostic biomarker and potential therapeutic target.

Table 1 (continued)

| Tumor type                  | Targets/ Regulators and Signaling Pathways | Cell line                          | Function                                                                                           | Reference |
|-----------------------------|-------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------|-----------|
| Chordoma                    | Smad3                                     | U-CH1 and U-CH2                    | ↑↑ miR-16-5p: proliferation, migration, invasion                                                   | [27]      |
|                             | LINC00662, RNF1448                        | U-CH1 and U-CH2                    | Δ LINC00662 (which sponges miR-16-5p): ↓ proliferation, migration, invasion, colony formation, and EMT process | [28]      |
| Gastric cancer              | PD-L1                                      | PBMCs and CD3+ T cells             | M1 Macrophage-Secreted Exosomes Carrying miR-16-5p: ↑ polarization of macrophages to its M1 phenotype, and T cell activation, ↓ PD-L1 expression | [29]      |
|                             | Smad3                                      | BSG823 and SGC-7901                | Melatonin treatment: ↑ miR-16-5p: ↓ proliferation, ↑ apoptosis                                      | [30]      |
|                             | LINC00649, YAP1, Hippo signaling pathway   | MGС-803 and SGC-7901               | Δ LINC00649 (which sponges miR-16-5p): ↓ proliferation, migration, viability, ↑ apoptosis         | [31]      |
| Lung cancer                 | WEE1                                       | GLC-82 and HTB-182                 | Quercetin: ↑↑ miR-16-5p → proliferation, colony formation, viability, ↑ apoptosis, and radiosensitivity | [32]      |
| Colorectal cancer           | Linc00210, PTK2                           | BEAS-2B, A549, Calu-3, H1299, SPCA-1, and PC-9 | Δ Linc00210 (which sponges miR-16-5p): ↓ proliferation, invasion, ↑ apoptosis                        | [33]      |
|                             | XIST, WEE1                                | H157, HCC827, A549 and H838        | Δ XIST (which sponges miR-16-5p): ↓ colony formation, viability, ↑ apoptosis, and radiosensitivity | [34]      |
| Colorectal cancer           | PVT1, VEGFA, VEGFR1, AKT signaling         | FHC, HCT116 and SW480, and HEK293T | Δ PVT1 (which sponges miR-16-5p): ↓ proliferation, migration, and invasion                         | [35]      |
| Erythroleukemia             | ITGA2                                      | Caco-2, SW480, SW620, LoVo, and HT29 | Quercetin: ↑↑ miR-16-5p → proliferation, migration, and invasion, ↑ apoptosis, and radiosensitivity | [36]      |
| Prostate cancer             | AKT3                                       | MEL cells                          | Quercetin: ↑↑ miR-16-5p → erythroid differentiation of MEL cells by regulating ribosome biogenesis   | [37]      |
| Chondrosarcomas             | VEGF-A, PIK/Akt signaling                 | J012, SW1353                       | Resistin treatment: ↓ miR-16-5p: ↑ VEGF-A-dependent EPCs angiogenesis                             | [38]      |
| Giant cell tumor of bone    | BMBCells                                   | BMBCells                           | ↑↑ miR-16-5p: ↓ RANKL-induced osteoclastogenesis                                                  | [39]      |
| Papillary thyroid carcinoma | SNHG12                                     | PTC cell lines                     | ↑↑ miR-16-5p: ↓ proliferation, migration, and invasion, ↑ apoptosis, and cell cycle distribution | [40]      |
| Renal cell carcinoma        | PVT1                                       | HK-2, A498, 786-O, ACHN and Caki-1 | Δ PVT1 (which sponges miR-16-5p): ↓ proliferation, migration invasion, EMT process, and ↑ apoptosis | [41]      |
| Bladder cancer              | BIMP1/NFkB signaling pathway               | T24 and 5637                      | ↑↑ miR-16-5p: ↓ viability, ↑ autophagy and apoptosis                                              | [42]      |
| Cholangiocarcinoma          | R-2HG, Erq, YAP1                          | QBG39, HuCCT1, and HEK293T         | IDH mutations: ↑ R-2HG production → degradation of FTO so ↓ protein translation of the ERα, ↑ miR-16-5p: ↓ YAP1: ↓ proliferation and cell growth | [43]      |
different cancers. Induction of DNA methylation in miR-16-5p is another mechanism of down-regulation of this miRNA in cancers [14]. Future studies are needed to find possible epigenetic alterations that affect transcription of precursor of miR-16-5p.

Different studies have shown the effects of miR-16-5p in regulation of chemosensitivity, radiosensitivity as well as response to the targeted therapy by sorafenib. From a clinical point of view, up-regulation of miR-16-5p is a potentially effective modality for suppression of tumor growth and defeating chemotherapy resistance. However, introduction of miR-16-5p mimic into cancerous cells needs a specific strategy to shield the miRNA mimics from self-hydrolysis or degradation by RNases. Without these considerations, the short half-life of naked RNA mimics reduces the potential effects of miRNAs [51]. Moreover, issues regarding the toxicity or nonspecific cell-targeting nature of miRNA carriers should be solved. These issues have attenuated the pace of entering miRNA mimics into the clinical setting.

Cumulatively, miR-16-5p is a putative tumor suppressor miRNA that can be used as a therapeutic modality in different cancers. However, the biosafety and bioavailability issues should be solved before introduction of this modality in clinical settings.

Table 2  Function of miR-16-5p or its partners in animal models (∆: knock-down or deletion)

| Tumor Type       | Animal models                                      | Results                                                                 | Reference |
|------------------|---------------------------------------------------|-------------------------------------------------------------------------|-----------|
| Neuroblastoma    | NOD.Cg-PrkdcscidIl2rgtm-1Wjl/SzJ (NSG) mice       | ↑↑miR-16-5p: ↓bioluminescence, tumor size, and tumor weight             | [7]       |
|                  | BALB/c nude mice                                  | ΔCirc-CUX1 (which suppresses miR-16-5p): ↓tumor size, tumor weight, and tumor growth | [8]       |
| Hepatocellular   | female BALB/c nude mice                           | ↑↑AGAP2-AS1: ↑tumor growth and metastasis                              | [11]      |
| carcinoma        | male BALB/c nude mice                             | ΔAGAP2-AS1: ↓tumor growth and metastasis                                | [13]      |
|                  | male BALB/c nude mice                             | ΔTTN-AS1 (which suppresses miR-16-5p): ↓tumor size, tumor weight, sorafenib resistance | [14]      |
|                  | male BALB/c nude mice                             | ΔSNHG22 (which suppresses the transcription of miR-16-5p): ↓tumor growth and angiogenesis | [14]      |
| Cervical cancer  | BALB/c nude mice                                  | ΔPDK4 (a target of miR-16-5p): ↑chemotherapy efficiency                | [16]      |
|                  | BALB/c nude mice                                  | ΔDLX6-AS1 (which sponges miR-16-5p): ↓tumor sizes, volumes, and weights | [25]      |
| Breast cancer    | BALB/c nude mice                                  | Δmir-16-5p: ↑tumor volume, proliferation and metastasis                | [17]      |
|                  | nude mice                                         | ↑↑mir-16-5p: ↓tumor growth                                             | [19]      |
|                  | BALB/c nude mice                                  | ΔATXN8OS (which sponges mir-16-5p): ↑tamoxifen sensitivity             | [20]      |
| Chordoma         | BALB/c athymic nude mice                          | ↑↑mir-16-5p: ↓tumor volume and proliferation                           | [27]      |
|                  | BALB/c nude mice                                  | ΔLINC00662 (which sponges miR-16-5p): ↓tumor volumes and tumor weight | [28]      |
| Gastric cancer   | BALB/c mice and NOD/SCID nude mice                | M1 macrophage-secreted exosomes carrying miR-16-5p: ↓tumor growth, volume and weight | [29]      |
|                  | female BALB/c nude mice                           | ΔLINC00649 (which sponges miR-16-5p): ↓tumor growth                   | [31]      |
|                  | female BALB/c-nude mice                           | ΔLINC00649 (which sponges miR-16-5p): ↓tumor growth, tumor weight prolifer, and metastasis | [32]      |
| Lung cancer      | nude mice                                         | ΔLINC00649 (which sponges miR-16-5p): ↓tumor growth, volume and weight | [34]      |
| Colorectal cancer| male BALB/c nude mice                             | ↑↑mir-16-5p: ↓tumor volume and weight                                 | [36]      |
|                  | male nude mice                                    | CuET treatment: ↓tumor volume and growth, ↑apoptosis                   | [37]      |
|                  | BALB/c nude mice                                  | ↑↑mir-16-5p: ↓tumor volume and growth                                  | [38]      |
| Chondrosarcoma   | male nude mice                                    | ↑↑Resistin: vessel markers VEGF-A and CD31, EPC markers CD34 and CD133, and vessel formation | [42]      |
| Bladder cancer   | male BALB/c nude mice                             | ↑↑miR-16-5p: ↓tumor volume, weight, and growth                         | [46]      |
| Cholangiocarcinoma| female nude mice                                  | ↑↑R-2HG (which increases levels of miR-16-5p): ↓tumor growth          | [48]      |
## Table 3: Dysregulation of miR-16-5p or its partners in clinical samples (NB: Neuroblastoma, FAM: fetal adrenal medulla, ANCTs: adjacent non-cancerous tissues, OS: Overall survival, TNM: tumor-node-metastasis, ccRCC: clear cell renal cell carcinoma)

| Tumor type                | samples                                                                 | Expression of miR-16-5p or other genes (Tumor vs. Normal) | Kaplan-Meier analysis (impact of miR-16-5p dysregulation) | Association of expression of miR-16-5p or expression of other genes with clinico-pathologic characteristics | Method by which RNA was detected | Reference |
|---------------------------|-------------------------------------------------------------------------|------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------|-----------|
| Neuroblastoma             | R2 database, containing 105 NB patients                                  | Down                                                      | Lower OS                                                  | Upregulation in circ-CUX1 was correlated with advanced TNM stage, low differentiation grade and lymph node metastasis. | SYBR® Premix Ex TaqTM Kit        | [7]       |
|                           | 50 pairs of tumor tissues and FAM tissues                                | Upregulation in circ-CUX1 (which sponges miR-16-5p)       | Lower OS                                                  | Upregulation in circ-CUX1 was correlated with advanced TNM stage, low differentiation grade and lymph node metastasis. | SYBR® Premix Ex TaqTM Kit        | [8]       |
| Osteosarcoma              | 40 pairs of tumor tissues and ANCTs                                      | Down                                                      | Lower OS                                                  | Upregulation in LINC00662 was correlated with distant metastasis, TNM stage, and tumor size.       | SYBR® Premix Ex Taq™             | [9]       |
|                           | 51 pairs of tumor tissues and ANCTs                                      | Upregulation in LINC00662 (which sponges miR-16-5p)       | Lower OS                                                  | Upregulation in LINC00662 was correlated with distant metastasis, TNM stage, and tumor size.       | SYBR® Premix Ex Taq™             | [23]      |
|                           | 30 pairs of tumor tissues and ANCTs                                      | Upregulation in hsa_circ_0005721 (which sponges miR-16-5p)|                                           |                                                                                                   |                                  |           |
| Hepatocellular carcinoma  | 137 pairs of tumor tissues and ANCTs                                    | Upregulation in AGAP2-AS1 (which sponges miR-16-5p)      |                                           | Upregulation in LINC00662 was correlated with large tumor size, metastasis, recurrence and high histological grade tissues | SYBR® Prime-ScriptTM RT-PCR Kit   | [11]      |
|                           | 100 pairs of tumor tissues and ANCTs                                    | Downregulation in miR-16-5p                               |                                           |                                                                                                   | SYBR® Green PCR kit              |           |
|                           | 60 pairs of tumor tissues and ANCTs                                    | Upregulation in SNHG22 (which suppresses transcription of miR-16-5p)| |                                           | SYBR® Green PCR kit | [14] |
| Cervical cancer           | 63 pairs of tumor tissues and ANCTs                                    | Upregulation in CARM1 (a target of miR-16-5p)            | Downregulation in miR-16-5p                             | Upregulation in CARM1 was correlated with higher clinical staging and poorer tumor differentiation | SYBR® Green PCR kit              | [15]      |
| Gliomas                   | 72 pairs of tumor tissues and ANCTs                                    | Downregulation in miR-16-5p                               |                                           |                                                                                                   | SYBR® Green I fluorescence method | [17]      |
|                           | GEO and TCGA databases                                                  | Upregulation in ANLN (a target of miR-16-5p)             | Downregulation in miR-16-5p                             |                                                                                                   | SYBR® Green kit                 | [18]      |
|                           | 40 pairs of tumor tissues and ANCTs                                    | Downregulation in miR-16-5p                               |                                           |                                                                                                   | SYBR® Premix Ex Taq™ reagent     | [19]      |
|                           | 22 pairs of tumor tissues and ANCTs                                    | Upregulation in ATXN8OS (which sponges miR-16-5p)        |                                           |                                                                                                   | TaqMan probe                     | [20]      |
| Gliomas                   | 79 patients with astrocytic gliomas and 9 non-neoplastic brain samples  | Downregulation in miR-16-5p                               |                                           |                                                                                                   |                                  |           |
| Tumor type               | samples                                                                 | Expression of miR-16-5p or other genes (Tumor vs. Normal) | Kaplan-Meier analysis (impact of miR-16-5p dysregulation) | Association of expression of miR-16-5p or expression of other genes with clinico-pathologic characteristics | Method by which RNA was detected          | Reference |
|-------------------------|------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------|-----------|
| Chordoma                | 12 chordoma tissues and 12 nucleus pulposus tissues 10 chordoma tissues and 3 nucleus pulposus tissues 30 pairs of tumor tissues and ANCTs | Downregulation in miR-16-5p                              |                                                          |                                                                                                                 | SYBR-Green PCR Master Mix               | [27]      |
| Gastric cancer          | 54 pairs of tumor tissues and ANCTs TCGA dataset                        | Downregulation in miR-16-5p                              |                                                          | Upregulation in LINC00662 (which sponges miR-16-5p) was correlated with a higher risk of lymphatic metastasis, a higher incidence of vascular cancer embolus, and advanced TNM stage. | RT2 SYBR Green FAST Mastermix or miScript SYBR Green PCR Kit | [28]      |
| Lung cancer             | 40 pairs of tumor tissues and ANCTs                                    | Upregulation in Linc00210 (which sponges miR-16-5p)      |                                                          | Upregulation in Linc00210 which sponges miR-16-5p was correlated with a higher risk of lymphatic metastasis, a higher incidence of vascular cancer embolus, and advanced TNM stage. | SYBR Premix Ex Taq                      | [31]      |
| Colorectal cancer       | 72 pairs of tumor tissues and ANCTs                                    | Upregulation in PVT1 (which sponges miR-16-5p)           | Lower OS                                                | Upregulation in PVT1 was significantly correlated with lymph node metastasis, distant metastasis, and TNM (tumor, node, metastasis) stage. | SYBR Green Master Mix                   | [32]      |
|                         | 42 pairs of tumor tissues and ANCTs GEO database: GSE75970, GSE74602, GSE89076, and GSE10950 | Upregulation in ALDH1A3 (a target of miR-16-5p)          | Lower OS                                                |                                                                                                                 | SYBR Green Master Mix                   | [33]      |
| Chronic lymphocytic leukemia | 224 CLL cases and 224 matched controls                  | miR-16-5p levels were unrelated to CLL risk.             |                                                          |                                                                                                                 | TaqMan probes                           | [34]      |
| Chondrosarcoma          | 9 human chondrosarcoma tissues and 9 normal cartilage                 | Downregulation in miR-16-5p                              |                                                          |                                                                                                                 | iTaq™ Universal SYBR Green Supermix    | [35]      |
| Giant cell tumor of bone | 17 GCT tissue and 4 cancellous bone as controls                      | Downregulation in miR-16-5p                              |                                                          |                                                                                                                 | SYBR Green Master Mix                   | [36]      |
| Ovarian cancer          | 142 ovarian cancer patients, and 97 healthy controls                 | Upregulation in miR-16-5p                                | No correlation between the gene expression levels, and the survival time |                                                                                                                 | SYBR Green Master Mix                   | [37]      |
Table 3 (continued)

| Tumor type            | samples          | Expression of miR-16-5p or other genes (Tumor vs. Normal) | Kaplan-Meier analysis (impact of miR-16-5p dysregulation) | Association of expression of miR-16-5p or expression of other genes with clinico-pathologic characteristics | Method by which RNA was detected | Reference |
|-----------------------|------------------|----------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------------|--------------------------------|-----------|
| Renal cell carcinoma  | 25 patients with ccRCC | Upregulation in PVT1 (which sponges miR-16-5p) | Upregulation in PVT1 was correlated with TNM stage, Fuhrman grade, lymph node metastasis and tumor size. | SYBR Green | [45] |

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Authors’ contributions

SGF wrote the manuscript and revised it, MT supervised and designed the study, TK, VS, STA and BMH collected the data and designed the figures and tables. All authors read and approved the submitted version.

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Data availability

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participant

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations.

Consent of publication

Not applicable.

Competing interests

The authors declare they have no conflict of interest.

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