

# Function of microRNA-145 and mechanisms underlying its role in malignant tumor diagnosis and treatment

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**Abstract:** miRNAs are single-stranded small RNAs that do not encode proteins. They can combine complementarily with the 3'-UTRs of target gene mRNA molecules to promote targeted mRNA degradation or inhibit mRNA translation, thereby regulating gene expression at the post-transcriptional level. MiRNAs participate in regulation of cell cycling, growth, apoptosis, differentiation, and stress responses. MiRNA-145 (miR-145) is a tumor suppressor that targets various tumor-specific genes and proteins, thereby influencing related signaling pathways. MiR-145 not only regulates tumor growth, invasion, and metastasis, but is also important for tumor angiogenesis and tumor stem cell proliferation. Here, we review the roles and mechanisms of miR-145 in the diagnosis and treatment of malignant tumors. Published data confirm that miR-145 expression in various tumors is significantly lower than that in normal tissues and that overexpression of miR-145 inhibits the growth of different tumor cells, significantly reduces the ability of tumors to spread, and improves sensitivity to chemotherapeutic drugs. We conclude that miR-145 is a potential marker for use in the early diagnosis and prognostic evaluation of patients with cancer, has a role as a tumor suppressor, and is a promising cancer treatment target candidate.

**Keywords:** miRNA-145, tumor, proliferation, metastasis, mechanism

## Introduction

The mechanisms underlying the occurrence and development of malignant tumors are of great research interest, particularly those that influence the pathogenesis, diagnosis, and treatment of tumors. Protein coding genes are the primary effectors and regulators of tumor occurrence and development; however, the emergence of epigenetics has revealed numerous regulatory mechanisms and effects on protein function that occur after gene transcription. Epigenetic control pathways involving non-coding RNA molecules are an area of increasing research interest, with specific relevance to miRNAs. MiRNAs are widespread in eukaryotic organisms, where they are closely associated with the expression and regulation of tumor-associated genes and influence the occurrence and development of tumors.<sup>1</sup>

MiRNAs are small, single-stranded RNA molecules that do not encode proteins.<sup>2</sup> Non-coding single-stranded RNA precursors, which are hairpin structures of approximately 70–90 nucleotides, are processed by the Dicer enzyme to produce miRNAs of about 22 residues. These miRNAs can be complementary with the 3'-UTRs of target mRNA molecules and they may promote degradation of target mRNAs or inhibit their translation, thereby mediating post-transcriptional gene regulation. MiRNAs

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can influence cell cycling, growth, apoptosis, differentiation, and stress responses, and are important as gene regulators, particularly in cancer.<sup>3,4</sup> Approximately 5,300 miRNA target genes have been reported to date, and 52.5% of known miRNAs are located in genome regions related to cancer or fragile sites;<sup>5,6</sup> a fragile site is a site-specific gap or fracture region that occurs in a metaphase chromosome when DNA synthesis is partially suppressed, which is susceptible to rearrangements in response to external factors, and predisposes cells to cancer. Fragile sites are usually stable in somatic cells; however, they are frequently absent or rearranged in tumor cells. By regulating target gene signaling pathways influencing tumor growth, invasion, metastasis, and angiogenesis, miRNAs can function as oncogenes or tumor suppressor genes.

miRNA-145 (miR-145) is a tumor suppressor expressed in various tumors, including prostate, bladder, colon, ovarian, and esophageal cancers, at lower levels than those in normal tissues.<sup>7-11</sup> As a tumor suppressor gene, miR-145 inhibits tumor cell proliferation, invasion, and metastasis,<sup>12,13</sup> increases tumor cell sensitivity to chemotherapeutic drugs,<sup>14</sup> and regulates tumor occurrence and development. Detailed studies suggest that miR-145 is potentially an ideal marker for diagnostic and prognostic evaluation of tumors and may represent a new cancer treatment target. This article reviews the reported roles of miR-145 in the diagnosis and treatment of malignant tumors and the mechanisms underlying these.

## Structure and biological characteristics of miR-145

MiR-145 maps to chromosome 5q32-33 and is 4.08 kb in length. The sequence is highly conserved, relative to other non-coding small molecule RNAs. Depending on the direction of transcription, the miR-145 locus can generate two transcripts, miR-145-3p (the passenger strand) and miR-145-5p (the guide strand). The miR-145-3p transcript is processed to produce miRNAs of ~22 nucleotides (miRBase database number: MIMAT0004601), whereas miR-145-5p generates 23 nucleotide fragments (miRBase database number: MIMAT0000437). MiR-145 maps in a cluster close to miR-143, and the two transcripts have similar roles and are thought to be co-transcribed.<sup>15</sup> The miR-145 chromosome locus is close to a very important tumor fragile site at 5q31, and implicated in tumor occurrence and development, as it is frequently deleted during the chromosome rearrangements that accompany malignant transformation, leading to its low expression levels in tumor tissues.<sup>6</sup>

MiR-145 was first detected in mouse heart,<sup>16</sup> and subsequently, in human colorectal cancer and other tissues.<sup>17</sup> Mesodermal tissues, such as the uterus, ovary, testis, prostate,

and heart, are relatively rich in miR-145;<sup>18</sup> however, the transcript is expressed at low levels in various tumor tissues, including colon, breast, prostate, lung, liver, bladder, and ovarian cancers, along with pituitary adenoma and B-cell lymphoma, among others.<sup>13</sup> There is evidence that miR-145 protects against tumorigenesis and can regulate tumor growth, invasion, metastasis, and angiogenesis via complete or incomplete complementation with the 3' non-coding region of target mRNA molecules, resulting in degradation of the target mRNAs and effects on their translation levels.

## MiR-145 and tumor cell growth

Both the sequence and tissue-specific transcription of miR-145 are highly conserved, and this miRNA regulates oncogene expression at the transcriptional and post-transcriptional levels, thereby reducing tumor growth by blocking the cell cycle and promoting tumor cell apoptosis.

MiR-145 exerts its effects on tumor cells through regulation of downstream target genes, including: octamer-binding transcription factor 4 (*OCT4*), SRY-box 9 (*SOX9*), *C-MYC*, *YES*, *EGFR*, insulin-like growth factor, mucin 1 (*MUC1*), adenovirus EIB19000 interaction protein 3, signal transducer and activator of transcription 1 (*STAT1*), tumor necrosis factor super family member 10 (*TNFSF10*), and others.<sup>19-24</sup> MiR-145 also regulates the differentiation of human embryonic stem cells and inhibits proliferation of smooth muscle cells by targeting *OCT4*, *SOX2*, and Krüppel-like factor 4 (*KLF4*).<sup>25</sup>

Cho et al showed that miR-145 negatively regulates the expression of the folate receptor and NUDT1 at the mRNA and protein levels, respectively,<sup>26</sup> and cell proliferation is inhibited in miR-145-transfected lung adenocarcinoma cells. Zhong et al<sup>27</sup> studied the expression of three different miRNAs in patients with non-small-cell lung cancer (NSCLC) and conducted quantitative analysis of three kinds of miRNA molecules; miR-145 was identified as mainly involved in regulating tumor cell behavior through the RAS/ERK and PI3K/AKT signaling pathways. Further, miR-145 and miR-143 attenuate tumor cell growth by inhibiting the ERK5/c-MYC and p68/p72/ $\beta$ -catenin signaling pathways in Apc(Min) mice with tumors of the gut.<sup>28</sup> Moreover, Xu et al showed that miR-145 inhibits tumor cell growth and angiogenesis in patients with colon cancer by targeting mammalian target of rapamycin (mTOR)/p70S6K1 signaling,<sup>29</sup> while Wang et al reported that overexpression of sentrin-specific protease 1 (SEN1), which promotes the proliferation, infiltration, and metastasis of tumor cells, is an important feature of bladder cancer<sup>30</sup> and, in a nude mouse model of bladder cancer, miR-145 inhibited tumor formation by interfering with SEN1.

## MiR-145 in tumor invasion and metastasis

Local invasion and distant metastasis are important characteristics of malignant tumors and the main cause of death from cancer, and miR-145 can regulate these processes.<sup>31</sup>

Sachdeva et al showed that miR-145 exerts its function in a cell-specific manner.<sup>32</sup> Although miR-145 inhibits cell growth in MCF-7 and HCT-116 cells, it has no significant effect on cell growth in metastatic breast cancer cell lines. However, miR-145 significantly suppresses cell invasion in these cells. Using luciferase reporter assays, they showed that miR-145 targets the tumor metastasis gene, *MUC1*, and inhibits tumor metastasis by silencing its expression. Gotte et al reported that miR-145 regulates the movement of breast cancer cells by targeting expression of the cell adhesion molecule, JAM-A, and the actin-crosslinking protein, fascin, which influence cell cytoskeletal rearrangement and nuclear rotation.<sup>33</sup>

MiR-145 also negatively regulates N-cadherin levels by binding directly to its 3'-UTR and overexpression of miR-145 silences N-cadherin expression, inhibiting invasion and metastasis of a lung adenocarcinoma cell line.<sup>34</sup>

## MiR-145 and tumor angiogenesis

Tumor angiogenesis has a key role in tumor growth and metastasis, along with patient prognosis. Tumor angiogenesis and anti-tumor angiogenesis are studied with the aim of cancer prevention and treatment, and many investigations have shown that miR-145 is important in this process.<sup>35</sup>

The miR-145 gene locus is close to that of miR-143 and, importantly, their transcription is coordinated.<sup>15</sup> Both transcripts directly participate in the regulation of vascular smooth muscle cell differentiation by maintaining the cell in a mature and shrinkable state.<sup>36</sup> Cordes et al reported that miR-145 and miR-143 control the expression of KLF4, myocardin, and Elk-1, thereby promoting the differentiation of vascular smooth muscle cells and inhibiting their proliferation.<sup>15</sup>

## MiR-145 and tumor stem cells

MiR-145 not only directly modulates the biological characteristics of tumor cells, but can also control tumor stem cells, a subset of tumor cells with stem cell characteristics, that are the source of tumor growth, metastasis, and recurrence. Targeting of tumor stem cells has become a new approach for cancer treatment. Xu et al reported that miR-145 regulates the expression of cell reprogramming genes, including *OCT4*, *SOX2*, and *KLF4*, which maintain stem cell function and have characteristics of oncogenes.<sup>25</sup> MiR-145 also inhibits human embryonic stem cell regeneration, promotes

their differentiation, and is important for tumorigenesis and tumor development. Simultaneously, *OCT4* inhibits miR-145 expression, forming an expression-regulation negative feedback loop. Research into this phenomenon will provide new information regarding the role of miR-145 in tumor stem cells, and it is of great significance for the treatment of tumors. A study of bone marrow cells showed that stable knockdown of miR-145 following its overexpression in CD34<sup>+</sup> cells can lead to myelodysplastic (5q-) syndrome.<sup>37</sup>

## Relationship between miR-145 and tumors

MiR-145 has been studied extensively in the context of tumor cell growth inhibition, and has become increasingly important in tumor diagnosis, prognostic assessment, and targeted therapy.<sup>38</sup> MiR-145 may function as a tumor suppressor gene that is expressed in various tumor tissues, including ovarian, cervical, breast, and colorectal cancers, at significantly lower levels than those in normal tissue.<sup>39-42</sup> Consequently, miR-145 is expected to be useful as an early tumor diagnostic and prognostic marker. In addition, overexpression of miR-145 inhibits the proliferation and metastasis of tumor cells, and it functions as a tumor suppressor gene and improves the sensitivity to chemotherapeutic drugs; hence, it is expected to serve as a novel target for cancer treatment.

## Progress in the diagnosis of malignant tumors by analysis of miR-145

Studies on associations of miR-145 with specific tumors are ongoing. As a diagnostic tool with high accuracy and efficiency, miR-145 has potential for application in tumor diagnosis; however, this approach remains at the research stage.<sup>43</sup>

MiR-145 may be an ideal marker for early diagnosis. Boufraqueh et al used reverse-transcription PCR (RT-PCR) to quantitatively detect miR-145 expression in 75 samples from cases with thyroid cancer, demonstrating that miR-145 expression levels were significantly higher in benign tissue than in malignancies.<sup>44</sup> Blood miR-145 levels are markedly increased in patients with thyroid cancer and show a specific gradient of venous concentration, suggesting that miR-145 may be useful as an accessory biomarker for thyroid carcinoma diagnosis. Moreover, Peng et al demonstrated that miR-145 and miR-378\* are potential early diagnostic markers of colorectal cancer.<sup>45</sup>

The clinical signs of malignant pleural mesothelioma (MPM) are difficult to distinguish from those of reactive mesothelial proliferation. Andersen et al used quantitative

RT-PCR to analyze 742 miRNA molecules in tumor tissues and corresponding non-neoplastic pleural mesothelial tissues, and found that levels of miR-145, miR-126, miR-143, and miR-652 were significantly reduced in tumor tissues and that these four miRNAs can be used as markers of MPM.<sup>46</sup>

Gits et al showed that miR-145 levels in liposarcomas were significantly lower than those in normal adipose tissue, with marked differences between different tumor subtypes, suggesting that miR-145 levels can be used for objective auxiliary diagnosis of liposarcoma.<sup>47</sup>

Ethnic variation in the usefulness of miR-145 as a marker for diagnosing tumors has been described, with the marker exhibiting higher sensitivity and specificity in Caucasian than East Asian patients in a meta-analysis, which demonstrates that miR-145 has high accuracy in distinguishing between patients with and without lymph node metastases of various cancers.<sup>43</sup>

MiR-145 levels are closely associated with prognosis of patients with cancer. Campayo et al determined miR-145 and miR-367 levels in tumor tissues from 70 patients with NSCLC, and found that the average time to recurrence for patients with low miR-145 levels was 18.4 months, whereas that for patients with high miR-145 levels was 28.2 months.<sup>48</sup> In contrast, the recurrence period for patients with high levels of miR-367 was shorter than that of patients with low levels. Hence, miR-145 and miR-367 levels can be used as predictors of postoperative recurrence in patients with NSCLC.

Wu et al showed that miR-145 targets matrix metalloproteinase-11 (MMP-11) to inhibit the proliferation and metastasis of renal cell carcinoma (RCC), suggesting that miR-145 could be used as an early predictor of RCC metastasis.<sup>49</sup>

Kim et al found that low levels of miR-145 are significantly correlated with recurrence and survival rates in patients with ovarian cancer (HR=8.62,  $P=0.039$ ), and low miR-145 expression levels were detected in ovarian cancer patients with poor prognosis.<sup>50</sup>

Levels of miR-145 in cervical cancer samples are significantly lower than those in adjacent non-cancer tissues, and low expression of miR-145 is closely associated with advanced International Federation of Gynecology and Obstetrics stage, lymph node metastasis, vascular infiltration, and shorter survival; hence, MiR-145 is a potential prognostic marker for cervical cancer.<sup>51</sup> Low miR-145 expression is also associated with the diameter and location of rectal cancer and esophageal carcinoma stage.<sup>52,53</sup>

Xia et al<sup>54</sup> reported that differences in expression levels of miR-130b, miR-145, and miR-223 in patients with adult

T cell lymphoma (ATL) are associated with differences in patient survival rates. Multivariate analysis indicated that low miR-145 levels are associated with deterioration of patients with ATL and closely related to poor prognosis in these individuals. Tang et al also showed that low miR-145 levels are closely related to invasion and metastasis in osteosarcoma and can be used as an independent prognostic marker.<sup>55</sup>

Naito et al reported high levels of miR-145 expression in patients with advanced stage scirrhus-type gastric cancer ( $P=0.0156$ ), and significant correlation of high miR-145 expression with adverse prognosis ( $P=0.0438$ ).<sup>56</sup>

Overall, these studies demonstrate that levels of miR-145 expression in patients with cancer are strongly correlated with prognosis. In the majority of tumor types, low miR-145 levels are associated with worse prognosis.

## Progress in miR-145 research aimed at treatment of malignant tumors

Various studies have reported targeting miR-145 and related genes and proteins for drug delivery, and the consequent inhibition of tumor cell proliferation and metastasis, pointing to new possibilities for tumor treatment.

Chondrosarcoma is the most common type of adult bone tumor. The effects of traditional chemotherapy and radiotherapy on this type of tumor are limited, hence the main treatment option is surgery. Mak et al reported that ETS variant 5 (ETV5) activates MMP-2 expression in chondrosarcoma, which enhances bone matrix resorption.<sup>57</sup> Levels of SOX9, ETV5, and MMP-2 in cells were significantly reduced by stable transfection of miR-145 into chondrosarcoma cells by lentivirus, demonstrating the potential of miR-145 for use in the clinical treatment of chondrosarcoma.

He et al showed that overexpression of prostate-specific transcript 1 (PCGEM1) promotes proliferation and metastasis of prostate cancer cells, along with resistance of tumor cells to chemotherapeutic agents. MiR-145 and PCGEM1 exhibit double-negative feedback regulation, where overexpression of miR-145 inhibits that of PCGEM1, indicating a potential new approach for treating prostate cancer by targeting miR-145 or PCGEM1.<sup>58</sup>

MiR-145 regulates expression of key factors (HIF2 $\alpha$ , VEGF, MMP-9, and CCND1) in RCC progression, and hence, enhanced miR-145 expression inhibits RCC progression.<sup>59</sup>

Li et al reported that miR-145 expression is significantly reduced in rectal cancer tissues and can effectively inhibit the proliferation and metastasis of rectal cancer cells.<sup>60</sup> This finding provides a theoretical basis for treating rectal cancer by targeting this tumor suppressor. Ibrahim et al evaluated

substitution therapy with miR-145 and miR-133a mediated by polyethylene imide in a colorectal cancer model, which had the therapeutic effect of promoting tumor cell apoptosis and inhibiting proliferation.<sup>61</sup>

Huang et al reported that miR-145 reduces the expression of various oncogenes and tumor biomarkers in pancreatic cancer cell lines, including SET nuclear proto-oncogene, replication protein A1, mini chromosome maintenance complex component 2, ATP-binding cassette, subfamily C1, non-erythrocyte-type  $\beta$ -membrane contractile protein (SPTBN1), and serine palmitoyltransferase long chain base subunit 1.<sup>62</sup> As these proteins function in tumor growth inhibition, miR-145 may be an ideal target for tumor therapy.

Restoration of miR-145 expression can effectively promote apoptosis of breast cancer cells expressing wild-type TP53 or estrogen receptor, suggesting that miR-145 therapy may be effective in patients with breast tumors expressing wild-type TP53- or estrogen receptor.<sup>63</sup>

MiR-145 levels are lower in NSCLC than in normal lung cells, and AP27i145 replication is negatively correlated with miR-145 expression. Oncolytic herpes simplex virus (HSV)-1 selectively inhibits cell proliferation and colony formation in samples from patients with NSCLC. The combination of AP27i145 and radiotherapy is more likely to kill cancer cells than either treatment alone; hence, oncolytic HSV-1, which is regulated by miR-145, is an effective target for treatment of NSCLC.<sup>64</sup>

When miR-145 and related genes are targeted for treatment, they can reduce or even counteract chemotherapeutic resistance to some drugs, making them ideal targets for cancer drug therapy. Zhong et al<sup>27</sup> showed that miR-145 has an important role in reducing the apoptosis tolerance of tumor cells and that its expression enhances sensitivity to chemotherapeutic drugs, such as gefitinib, in patients with NSCLC.

Cioce et al<sup>20</sup> reported that cell invasiveness and resistance to the chemotherapeutic drug, pemetrexed, decreased in an MPM cell line overexpressing miR-145. Elevated OCT4 levels are considered one of the most important indices of cancer cell chemotherapy resistance; however, increased miR-145 levels can diminish expression of OCT4 and its target gene *ZEB1*, thus offsetting the rise in OCT4 levels caused by pemetrexed treatment.

Pancreatic cancer is a major cause of cancer deaths worldwide. Despite recent progress in research and treatment, difficulty in early disease detection and lack of effective treatments mean that the prognosis for patients with this type of cancer remains poor. Gemcitabine is a first-line drug for pancreatic cancer; however, chemotherapy resistance is a serious

problem. Lin et al showed that p70S6K1 has an important role in drug resistance.<sup>14</sup> Acting as a tumor suppressor, miR-145 directly inhibits p70S6K1 expression in pancreatic cancer, constituting an effective treatment regimen. Khan et al found that miR-145 inhibits the proliferation and metastasis of pancreatic cancer cells and improves sensitivity to gemcitabine. MiR-145 may target the *MUC13* 3'-UTR, thereby inhibiting intracellular MUC13 and downstream ERBB2 expression.<sup>65</sup>

Zhu et al reported that miR-145 is imported into ovarian cancer SKOV3/PTX cells, decreasing intracellular levels of cyclin-dependent kinase 6 and SP1,<sup>66</sup> levels of ATP binding cassette subfamily B1 and retinoblastoma 1 also decrease in response to miR-145. These changes could induce aggregation of antitumor drugs in cells, and a G1 cell cycle blockade, consequently improving the sensitivity of tumor cells to taxol in vitro and in vivo. In addition, reactivation of miR-145 expression by demethylation mediated by the DNA methylase inhibitor, 5-Aza-2'-deoxycytidine, may also increase susceptibility of tumor cells to taxol.

## MiR-145 regulatory factors

### Environmental factors influencing miR-145 expression

Various factors affect the expression of miR-145 and regulate the proliferation and metastasis of tumor cells and their sensitivity to chemotherapeutic drugs. MiR-145 expression levels are affected by carcinogens in a rat model, with expression in lung tissues decreasing significantly after 28 days of exposure to environmental cigarette smoke. MiR-145 is also regulated in response to stress, as well as cell apoptosis, proliferation, and angiogenesis.<sup>67</sup> Hepatitis B virus (HBV) infection promotes cell proliferation, reduces miR-145 expression, and participates in regulating cell transformation, leading to HBV-associated hepatocellular carcinoma (HCC).<sup>68</sup>

### Factors regulating transcription and processing of miR-145

The tumor protein, P53, and forkhead box O1/3 (FOXO1/3) promote transcription of precursor miR-145 (pre-miR-145), whereas Ras-responsive element-binding protein 1 (RREB1) and CCAAT/enhancer-binding protein- $\beta$  inhibit its transcription. During miR-145 maturation, P53 and breast cancer 1 proteins have catalytic roles, whereas the human RNA methyltransferase, BCDIN3, is inhibitory.<sup>69</sup> P53 primarily functions in Drosha-p68 complex formation to promote pri-miRNA shearing into pre-miRNAs; however, mutated P53 lacks this function, leading to inhibition of miR-145 expression.



Adjustment of colon cancer-associated transcript-2 (CCAT2) levels regulate miR-145 expression in the HCT-116 and HT-29 rectal cancer cell lines, confirming that CCAT2 is a negative regulator of miR-145. CCAT2 is enriched in the nuclei of HCT-116 cells and closely associated with pre-miR-145 expression. CCAT2 selectively inhibits miR-145 maturation in vitro by diminishing pre-miR-145 export to the cytoplasm by the Dicer enzyme, preventing pre-miR-145 shearing.<sup>70</sup>

In lung cancer cells, EGFR downregulates miR-145 expression via the ERK1/2 pathway.<sup>71</sup> MiR-145 expression regulation can be achieved through hypermethylation of the miR-145 promoter region in esophageal squamous cell carcinoma (ESCC).<sup>72</sup>

## Mechanisms underlying miR-145 function

Tumor development is a complex process involving multiple factors and stages, and the accumulation of multiple gene mutations. Consequently, the causes and mechanisms underlying the infinite proliferation of tumor cells are highly complex and include inactivation of tumor suppressor genes, overexpression of oncogenes, uncontrolled cell cycling, and tolerance to apoptosis. MiR-145 inhibits tumor growth by reducing oncogene expression, blocking of the cell cycle, and promoting tumor cell apoptosis. One important reason for the rapid proliferation of tumor cells is the activation of proto-oncogenes; miR-145 targets and inhibits multiple oncogenes or proteins, including c-MYC, FLI1, YES, and IRS-1, thereby exerting a tumor growth inhibitory effect.

MiRNAs have multiple downstream targets, and different miRNAs may act on the same target. Lee et al reported that high miR-145 expression diminishes levels of tumor metastasis-related gene expression, including *ADAM22*, *SPOCK3*, *PLAUR*, *SLC7A5*, and *FASCN1*.<sup>73</sup>

## MiR-145 targeted oncogenes

Sachdeva et al showed that P53 inhibits c-MYC expression via miR-145 and proposed the theory that miR-145 blocks the cell cycle.<sup>74</sup> According to this theory, P53 regulation of P21 is an important pathway that blocks the cell cycle; P21 expression is inhibited in tumor cells due to high expression of c-MYC, thus blocking the P53/P21 signaling pathway. When miR-145 expression is restored, c-MYC levels decrease and the inhibition of P21 is relieved, thereby restoring P53/P21 signaling.

Kent et al reported that miR-143 and miR-145 are involved in positive feedback loops in the *RAS* cancer gene signaling pathway.<sup>75</sup> MiR-143 inhibits expression of the *RAS*

subtype, *KRAS*, while miR-145 represses *RREB1* expression. In contrast, *RREB1* inhibits the miR-143/145 promoter and reduces miR-143/145 expression, and low miR-143/145 expression levels are important for *KRAS*-mediated cell transformation.

MiR-145 has a tumor-inhibiting effect; however, the mechanisms underlying its involvement in the proliferation, metastasis, and invasion of tumor cells are not entirely clear. Patients with bladder cancer express low levels of miR-145, which inhibits tumor cell proliferation by targeting *FSCN1*.<sup>8</sup> In prostate cancer, miR-145 inhibits the proliferation, invasion, and metastasis of tumor cells via the same target.<sup>76</sup>

## MiR-145 targeted apoptosis-related factors

Methylation of the miR-145 promoter in RCC results in low levels of this miRNA in this type of cancer. Expression of high miR-145 levels in RCC cells leads to inhibition of tumor cell proliferation and markedly increases cisplatin-induced apoptosis, possibly by inhibiting the expression of *ADAM17*, *c-MYC*, or other downstream genes.<sup>77,78</sup>

MiR-145 expression levels directly affect the tolerance of tumor cells to apoptosis-stimulating factors. Ostensfeld et al reported that overexpression of miR-145 in urothelial carcinoma cells strongly induced apoptosis, and that it simultaneously activated caspase-dependent and non-caspase-dependent apoptotic pathways. It has been speculated that the low levels of miR-145 expression in urothelial carcinoma may be one reason for tumor-induced apoptosis escape.<sup>79</sup>

MiR-145 also inhibits the proliferation of tumor cells in NSCLC by targeting c-MYC.<sup>80</sup>

Wang et al showed that miR-145 levels are significantly lower in MCF-7 breast cancer cells compared with normal mammary epithelial (MCF10A) cells.<sup>81</sup> RTKN expression is decreased in MCF-7 cells, indicating that miR-145 inhibits the proliferation of breast cancer cells by targeting RTKN.

DNA fragmentation is an important feature of apoptosis, which primarily occurs as a result of DFF40 degradation of chromosomal DNA. Under normal circumstances, DFF40 and DFF45 are bound to one another in the cell in an inactive state. When apoptosis occurs, a series of enzymes promote a cascade, comprising the activation of caspase-3, cleavage of DFF45 by activated caspase-3, and release of DFF40, leading to DNA fragmentation. Zhang et al reported that miR-145 directly inhibits DFF45 expression, thereby causing DNA fragmentation and inducing apoptosis in colon cancer.<sup>82</sup>

## Other tumor-related factors targeted by miR-145

MiRNAs can also contribute to disorders involving the onset and development of cancers. MiR-145 expression is significantly decreased in HCC cell lines and negatively correlated with high levels of insulin receptor substrate 1 (IRS1), a key factor in the tumorigenic insulin-like growth factor pathway. IRS1 is a direct target of miR-145, and increased miR-145 expression inhibits tumor cell proliferation by lowering IRS1 levels and inhibiting the downstream AKT/FOXO1 signaling pathway. The lower miR-145 expression in HCC has been suggested as a potential molecular mechanism underlying carcinogenesis.<sup>83</sup>

MiR-145 inhibits the invasion of U87 glioma cells by inhibiting the RhoA/ROCK1 pathway, where ROCK1, a newly discovered miR-145 target, promotes invasion of glioma cells.<sup>84</sup>

## Tumors in which miR-145 is overexpressed

MiR-145 is also overexpressed in a few tumor types, including esophageal adenocarcinoma (EAC) and glioma, where it enhances cell proliferation, invasion, and metastasis. In one study, no significant difference was observed in cell

proliferation or 5-fluorouracil resistance between an miR-145 EAC cell line treatment and control groups, and miR-145 enhanced the resistance of SK-GT-4 cells to cisplatin. There were clear differences in cell invasion, adhesion, and anti-apoptosis effects in the OE33, FLO-1, and SK-GT-4 cell lines, and invasion in the miR-145 treatment group was significantly greater than that in the control group. MiR-145 overexpression in ESCC prevents tumor cell proliferation and invasion, whereas overexpression of miR-145 in EAC enhances invasion and anti-apoptosis effects.<sup>85</sup>

MiR-145 expression is increased, and that of srGAP1 decreased, in invasive glioblastoma (IM3) cells, whereas downstream G-proteins remain active, thus promoting an invasive phenotype.<sup>86</sup>

## Summary

The known common tumor-related factors that miR-145 can target are as follows: PI3K/AKT,<sup>27</sup> ROCK1,<sup>87</sup> caspase,<sup>79</sup> c-MYC,<sup>74</sup> RTKN,<sup>81</sup> RREB1,<sup>75</sup> ER-alpha,<sup>63</sup> DFF45,<sup>82</sup> MUC1,<sup>32</sup> JAM-A,<sup>33</sup> fascin,<sup>33</sup> ELK1,<sup>15</sup> OCT4,<sup>25</sup> SOX2,<sup>25</sup> KLF4,<sup>25</sup> YES,<sup>21</sup> STAT1,<sup>21</sup> IRS-1,<sup>22</sup> FLI1,<sup>88</sup> and TNFSF10.<sup>11</sup> MiR-145 target molecules differ in various types of tumor and tissue. Target molecules and effects of their targeting by miR-145 in common tumors are presented in Table 1.

**Table 1** MiR-145 target molecules and consequences of their targeting in common tumors

Tumor type	Target molecule	Effect	Reference
Thyroid cancer	PI3K/AKT	Differentiation, proliferation, invasion, metastasis	44
Non-small-cell lung cancer	AEG-1/MTDH	Invasion, metastasis	89
	PI3K/AKT, RAS/ERK	Differentiation, proliferation, invasion, metastasis	27
	Oncolytic HSV-1	Sensitivity	64
Lung adenocarcinoma	c-Myc	Proliferation	80
	OCT4	Proliferation, endothelial-mesenchymal transition	90
	FR, NUDT1	Differentiation, proliferation, invasion, metastasis	26
	N-cadherin	Invasion, metastasis	34
Liver cancer	ADAM17	Proliferation	91
	IRS1	Proliferation	83
Pancreatic cancer	MUC13/HER2	Proliferation, invasion	66
	MUC13, ERBB2	Proliferation, invasion, sensitivity	65
	p70S6K1	Sensitivity	14
	SET, RPA1, MCM2, ABCC1, SPTBN1, SPTLC1	Proliferation	62
Colorectal cancer	PPAR- $\gamma$ /SOX9	Differentiation	23
	mTOR/p70S6K1	Proliferation, angiogenesis	29
	DFF45	Proliferation	82
	FLI1	Invasion, metastasis	88
	YES, STAT1	Proliferation	21
Gastric cancer	IRS-1/ $\beta$ -actin	Proliferation	92
Gut tumors	ERK5/c-Myc, p68/p72/ $\beta$ -catenin	Proliferation	28

(Continued)

**Table 1** (Continued)

Tumor type	Target molecule	Effect	Reference
Bladder cancer	IGF-1R/PAK1	Proliferation, invasion	93,94
	SENP1	Proliferation, invasion, metastasis	30
	FSCN1	Proliferation	76
Renal cell carcinoma	MMP-11	Proliferation, invasion	49
	HIF2 $\alpha$ /VEGF/MMP9/CCND1	Invasion, metastasis	59
	ADAM17, c-Myc	Proliferation, sensitivity	77,78
Prostate cancer	TNFSF-10	Proliferation	29
	PCGEM1	Proliferation, invasion, metastasis, sensitivity	58
	FSCN1	Proliferation, invasion, metastasis	8
Urothelial cancer	Caspase	Proliferation	79
Breast cancer	MUC1	Invasion, metastasis	81
	JAM-A, fascin	Metastasis	33
	RTKN	Proliferation	81
	ER-alpha	Proliferation	63
Ovarian cancer	MTDH	Proliferation	95
	Cdk6, Sp1, ABCB1, Rb1	Sensitivity	66
Osteosarcoma	ROCK1	Proliferation, invasion	87
Chondrosarcoma	SOX9, ETV-5, MMP-2	Metastasis	57
Pleural mesothelioma	OCT4/ZEB1	Proliferation, invasion, sensitivity	20
Glioma	RhoA/ROCK1	Invasion	84
Invasive glioblastoma	srGAP1	Invasion	86

MiR-145 not only regulates tumor growth, invasion, and metastasis, but also plays an important role in tumor angiogenesis and tumor stem cells; hence, with further research, miR-145 has potential for application as a treatment tool in clinical oncology.

## Conclusion

In summary, miR-145 has important functions in the proliferation, apoptosis, invasion, and metastasis of tumor cells. This is evidenced by findings showing that miR-145 is downregulated in numerous tumors compared with normal tissues, and that overexpression of miR-145 inhibits the growth of multiple tumor cells and functions as a tumor suppressor gene. Consequently, miR-145 is expected to be a marker for the early diagnosis and prognostic assessment of tumors. Furthermore, transfection with miR-145 can inhibit the proliferation and metastasis of tumor cells and improve sensitivity to chemotherapeutic drugs, potentially providing new tumor treatment approaches. The majority of studies of miR-145 in malignant tumors have been limited to investigation of its expression spectrum and its specific targets vary among tumors and have differing effects. The detailed mechanisms of miR-145 target gene activity, and the interactions among target genes in the context of tumorigenesis and development, have yet to be fully elucidated, and further study is required to better understand how miR-145 participates in tumor occurrence and development. Nevertheless, continuous

improvements in understanding and in-depth research into miR-145 and its potential as a diagnostic marker bring hope for novel interventions to overcome chemotherapy resistance and develop targeted biological therapies for the diagnosis and treatment of cancers.

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## Disclosure

The authors report no conflicts of interest in this work.

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