

# miR-152 as a tumor suppressor microRNA: Target recognition and regulation in cancer (Review)

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**Abstract.** MicroRNAs (miRNAs or miRs) are endogenous translation repressors of protein-coding genes that act by binding to the 3'-untranslated region of their target genes, and may contribute to tumorigenesis by functioning as oncogenes or tumor suppressor genes. miR-152, a member of the miR-148/152 family, is aberrantly expressed in various diseases, including various types of cancer. A growing body of evidence has demonstrated that miR-152 may act as a tumor suppressor gene by regulating its target genes, which are associated with cell proliferation, migration and invasion in human cancer. In the present review, the gene structure and functions of miR-152 are discussed, and in particular, its regulatory mechanism, experimentally validated targets and tumor suppressor role in cancer, are highlighted.

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## 1. Introduction

MicroRNAs (miRNAs or miRs) are small, endogenous, non-coding RNAs that act as post-transcriptional regulators by binding to the 3'-untranslated region (UTR) of their target messenger (m)RNAs, resulting in the degradation of the mRNA or its translational inhibition (1-5).

miRNAs are 18-25 nucleotides in length, and are generated by cytoplasmic RNase III Dicer from 70-100 nucleotides-long endogenous hairpin pre-miRNA precursors (2-5). miRNAs have been highly conserved during evolution (6). Presently, ~2,588 human mature miRNAs have been deposited in the miRBase (release 21, <http://www.miRBase.org/>). Accumulating evidence indicates that miRNAs influence a variety of cellular functions, including proliferation, differentiation and apoptosis (3,4,7). Furthermore, an increasing number of miRNAs have been implicated in a variety of diseases such as cancer (3). According to their function and expression pattern, miRNAs may act as oncogenes or tumor suppressors in cancer development and progression (3,7).

miR-152 is one of the miRNAs that have attracted great interest in recent years, since it is implicated in various types of cancer (8,9). Thus, it is of considerable significance to understand the regulation and function of miR-152 in human cancer. In the present study, the current knowledge of the functions of miR-152 in cancer is reviewed, with an emphasis on its regulation, targets and tumor suppressor role in human cancer.

## 2. Biogenesis and evolution of miR-152

miR-152 was first identified in mouse colon by tissue-specific cloning in 2002 (10). miR-152 is a member of the miR-148/152 family, which includes miR-148a, miR-148b and miR-152. Notably, in humans, the miR-152 gene is located on chromosome 17q21.32 (Fig. 1), within intron 1 of the coatmer protein complex, subunit zeta 2 (COPZ2) gene, and a CpG island is typically observed around its promoter region (8,9,11). Following transcription and cleavage by Drosha, pre-miR-152 is transported to the cytoplasm, where it is further processed by Dicer to form a miR-152 duplex (5). Two different mature miR-152 sequences, namely miR-152-5p and miR-152-3p, appear to be excised from opposite arms of the miR-152 duplex (Fig. 2). miR-152-3p, which is excised from the 3' arm

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**Key words:** miR-152, tumor suppressor, hypermethylation, human cancer

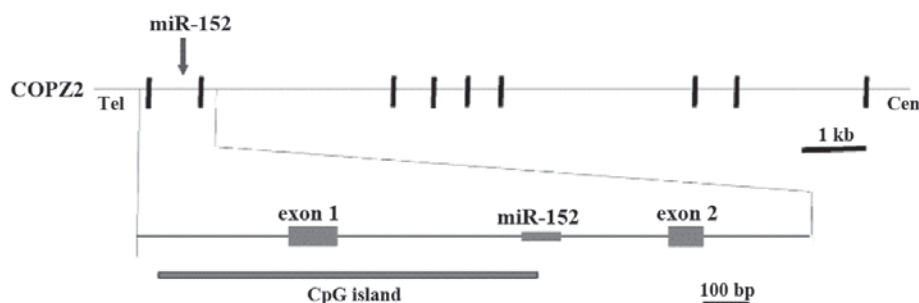


Figure 1. Structure of the genomic locus of human microRNA-152. The positions are designated according to the information in Epigenomics and Map Viewer for the coatomer protein complex, subunit zeta 2 gene, available at <http://www.ncbi.nlm.nih.gov/gene/51226>. miR, microRNA; COPZ2, coatomer protein complex, subunit zeta 2; Tel, telomere; Cen, centromere; kb, kilobase; bp, base pairs.

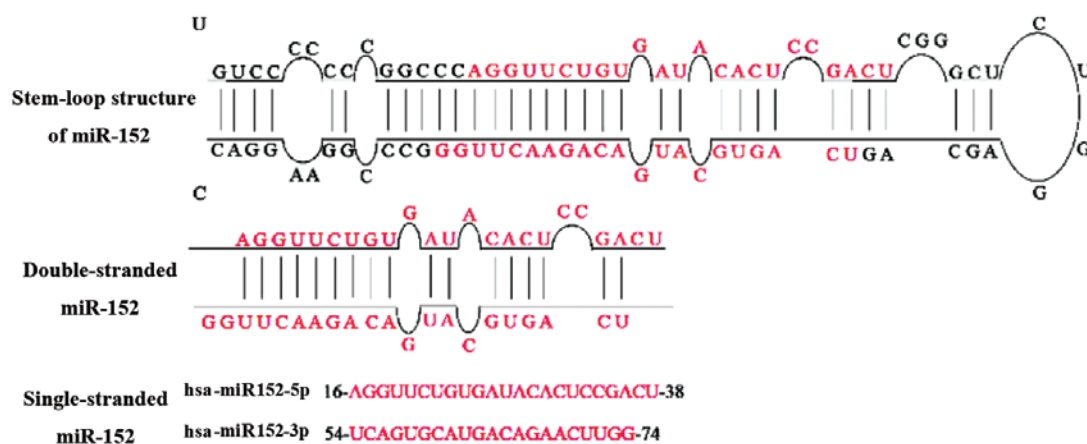


Figure 2. Biogenesis of miR-152. Two different mature miR-152 sequences, namely miR-152-5p and miR-152-3p, appear to be excised from opposite arms of the miR-152 duplex. miR, microRNA; hsa, *Homo sapiens*.

of the hairpin precursor, has been detected in more species than miR-152-5p.

The expression of miR-152 has been demonstrated in several species, according to miRBase (<http://www.mirbase.org/>). It is noteworthy that the mature miR-152 exhibits identical sequence in different species (with the exception of the extension at its 3' end), and also shares an identical seed sequence across various species (Fig. 3A), which suggests that miR-152 is important in certain gene regulatory networks. To assess the degree to which miR-152 is conserved across species, a neighbor-joining (NJ) tree was constructed in 10 representative animal species by using genomic DNA sequences retrieved from miRBase (Fig. 3B). The miR-152 NJ tree clearly revealed the existence of two main lineages, one of which contains *Homo sapiens*, *Canis familiaris*, *Ovis aries*, *Sus scrofa*, *Mus musculus*, *Bos taurus*, *Monodelphis domestica* and *Pan troglodytes*, while the other lineage comprises *Fugu rubripes* and *Danio rerio*. These findings suggest that miR-152 is evolutionarily conserved and the recent lineage-specific miR-152 may be common to the old ancestral processor.

### 3. Experimentally validated targets of miR-152 in human cancer

The identification of miRNA targets and their regulatory sequences is a complex problem in miRNA research, and

a considerable number of methods have been established to attempt such an identification, which are classified into computational (*in silico*) and experimental methods (12,13). The prediction of miRNA targets using the current algorithms implemented in computational methods always results in a large number of false signals that do not reflect the situation *in vivo*; therefore, the predicted miRNA targets must be validated experimentally (12).

Hundreds of genes have been proposed as candidate targets of miR-152 with high scoring when predicted by computational programs such as PicTar (<http://pictar.mde-berlin.de/>) and TargetScan (<http://www.targetscan.org/>). A number of these genes have been further confirmed experimentally as targets of miR-152 (Table I). Braconi *et al* (14) first described that the DNA methyltransferase 1 (DNMT1) gene is a direct target of miR-148a and miR-152 by using luciferase reporter constructs, which revealed that miR-152 could target the 3'-UTR of DNMT1, resulting in a significant reduction of DNMT1 at both mRNA and protein levels. This finding was further confirmed in subsequent studies on ovarian cancer (15), endometrial cancer (9), nickel sulphide (NiS)-induced cell malignant transformation (16), breast cancer (17), hepatitis B virus-related hepatocellular carcinoma (18), pancreatic cancer (19) and prostate cancer (20). In addition, E2F transcription factor 3, mesenchymal to epithelial transition (MET), rapamycin-insensitive companion

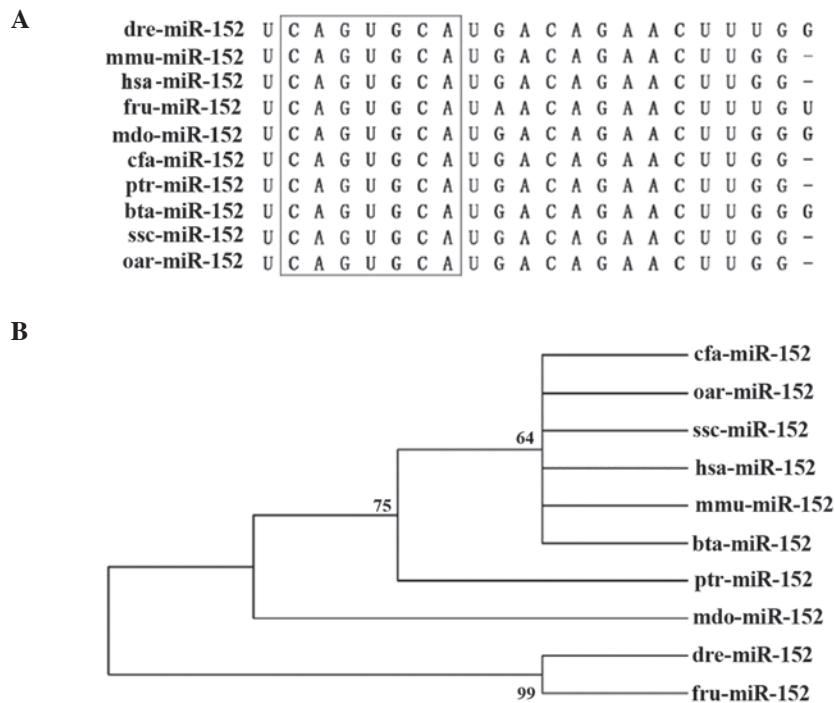


Figure 3. Conservation of miR-152 across species. (A) Sequence alignment of the mature miR-152 sequence in 10 different species. Seed sequences are highlighted in the black box. (B) Phylogenetic tree of miR-152. Numbers on each branch refer to the degree of reliability. miR, microRNA; hsa, *Homo sapiens*; cfa, *Canis familiaris*; oar, *Ovis aries*; ssc, *Sus scrofa*; mmu, *Mus musculus*; bta, *Bos taurus*; mdo, *Monodelphis domestica*; ptr, *Pan troglodytes*; fru, *Fugu rubripes*; dre, *Danio rerio*.

of mechanistic target of rapamycin (9), insulin-like growth factor 1 receptor (IGF-1R), insulin receptor substrate 1 (IRS1) (17), a disintegrin and metalloproteinase metalloproteinase domain 17 (ADAM17) (21,22), Kruppel-like factor 4 (KLF4) (23), fibroblast growth factor 2 (FGF2) (24), wntless-related integration site (Wnt1) (25), cluster of differentiation (CD) 151 (26), matrix metalloproteinase 3 (MMP3) (27) and transforming growth factor alpha (28) have been identified as targets of miR-152 in a wide array of human malignancies.

#### 4. miR-152 as a tumor suppressor miRNA in cancer

Particular miRNAs may act as oncogenes or tumor suppressors depending on their expression pattern and function (3,6). Those miRNAs with increased expression in tumor cells may be regarded as oncogenes, whereas down-regulated miRNAs are considered as tumor suppressors (29).

There has been a rapid increase in the number of publications focusing on miR-152 in recent years, which revealed that the expression of miR-152 was inhibited in a variety of tumors, including ovarian (15), endometrial (9) and breast cancer (17). These findings suggest that miR-152 may potentially function as a tumor suppressor in human cancer. The main aim of the present review was to understand how miR-152 interacts with its target genes and to identify the potential role of miR-152 in cancer.

*miR-152 mediates hypermethylation of DNA and its CpG island in human cancer.* Aberrant DNA hypermethylation of tumor suppressor genes, global DNA hypermethylation (GDM) and disruption of histone modification patterns are the three most important epigenetic changes contributing to the

malignant phenotype (30). In particular, DNA hypermethylation may be important in the initiation of multiple types of cancer (30,31). Huang *et al* (18) first reported that inhibition of miR-152 could functionally result in GDM in hepatitis B virus-related hepatocellular carcinoma cell lines. Using liquid chromatography-mass spectrometry (MS)/MS, the authors identified that the overexpression of miR-152 reduced GDM from 6.31 to 4.08% in the HepG2 2.2.15 cell line, whereas miR-152 inhibitor increased GDM from 4.55 to 5.88% in HepG2 cells. Underexpression of miR-152 also increased the DNA methylation level of the promoter region of tumor suppressor genes such as glutathione S-transferase pi 1 and cadherin 1 in these cells (18). Azizi *et al* (19) demonstrated that the overexpression of miR-152 decreased GDM to normal patterns in pancreatic cancer cell lines and restored the expression of tumor suppressor genes, including B-cell lymphoma 2/adenovirus E1B 19 kDa interacting protein 3 and secreted protein acidic and cysteine rich, by 3.8 and 2.9-fold, respectively. These data support a tumor suppressor role of miR-152 in the epigenetic aberration observed in cancer.

An increasing number of publications indicate that epigenetic silencing of tumor suppressor miRNAs by CpG island hypermethylation is a common feature of different types of human cancer (31,32). Hypermethylation of the CpG island of miR-152 has been detected in 70 (97.1%) cases of primary endometrial cancer (9). The concordance between DNA hypermethylation around the CpG island and underexpression of miR-152 was observed in 100% of the cases of primary endometrial cancer (9). These results suggest that the hypermethylation of the CpG island of miR-152 may downregulate its expression, and may be involved in endometrial cancer. Due to the hypermethylation of its CpG island, silencing of

Table I. Experimental confirmed targets of microRNA-152 in different types of cancer.

Cancer	Expression	Biological process	Target gene	Refs.
Endometrial cancer	Downregulation	Inhibited cell growth	DNMT1, E2F3, MET, RICTOR	(9)
Cholangiocarcinoma	Downregulation	Reduced cell proliferation	DNMT1	(14)
Ovarian cancer	Downregulation	Reduced cell proliferation	DNMT1	(15)
NiS-induced cell malignant transformation	Downregulation	Inhibited cell growth	DNMT1	(16)
Breast cancer	Downregulation	Inhibited cell proliferation, colony formation and tumor angiogenesis	DNMT1, IGF-1R, IRS1	(17)
Hepatocellular carcinoma	Downregulation	Reduced cell proliferation	DNMT1, Wnt1	(18,25)
Pancreatic cancer	Downregulation	Inhibited cell proliferation	DNMT1	(19)
Prostate cancer	Downregulation	Decreased cell growth, migration	DNMT1, TGF $\alpha$	(20,28)
NSCLC	Downregulation	Reduced cell proliferation, colony formation, migration and invasion	ADAM17, FGF2	(22,24)
Glioblastoma	Downregulation	Reduced cell proliferation, migration, invasion and pro-apoptosis	KLF4	(23)
Gastric cancer	Downregulation	Inhibited cell proliferation and motility	CD151	(26)
Glioma	Downregulation	Reduced invasion and invasion	MMP3	(27)
Neuroblastoma	Upregulation	Increased neuroblast differentiation and apoptosis	CHUK, CUL5, GADD45A	(36)

NSCLC, non-small cell lung cancer; NiS, nickel sulphide; DNMT1, DNA methyltransferase 1; E2F3, E2F transcription factor 3; MET, mesenchymal to epithelial transition; RICTOR, rapamycin-insensitive companion of mechanistic target of rapamycin; KLF4, Kruppel-like factor 4; ADAM17, a disintegrin and metalloproteinase metalloproteinase domain 17; FGF2, fibroblast growth factor 2; IGF-1R, insulin-like growth factor 1 receptor; IRS1, insulin receptor substrate 1; Wnt1, wingless-related integration site 1; CD151, cluster of differentiation 151; MMP3, matrix metalloproteinase 3; TGF $\alpha$ , transforming growth factor alpha; CHUK, conserved helix-loop-helix ubiquitous kinase; CUL5, cullin 5; GADD45A, growth arrest and DNA-damage-inducible, alpha.

miR-152 expression and overexpression of DNMT1 were also observed in NiS-transformed cells (16), breast cancer (17) and prostate cancer (20). Notably, there may be a crucial functional crosstalk between miR-152 and DNMT1 via a double-negative feedback regulatory loop, as speculated by Ji *et al* (16) regarding the classic ‘chicken and egg’ argument. DNMT1 exerts a crucial role in setting up and maintaining DNA methylation patterns in eukaryotic cells (33). Once increased expression of DNMT1 (‘egg’) occurs, DNMT1 is recruited to the miR-152 CpG island promoter, where it increases DNA methylation, contributing to reduced miR-152 expression (‘chicken’) (16). Furthermore, downregulated expression of miR-152 further increases DNMT1 expression by reduced targeting on DNMT1 3'-UTR (14-20). Therefore, epigenetic regulation of miR-152/DNMT1 may be important in tumorigenesis. In mixed lineage leukemia-rearranged infant acute lymphoblastic leukemia, hypermethylation of the CpG island of miR-152 was reported to be strongly correlated with a poor clinical outcome (34). Overall, hypermethylation of miR-152 may be considered as an epigenetic biomarker in human cancer.

*miR-152 and its targets are associated with cell proliferation in cancer.* miRNAs with antiproliferative and pro-apoptotic activity are likely to function as tumor suppressor genes (35). Antisense oligonucleotides targeting miRNAs have been used

to identify miRNA functions (36). In those studies, the inhibition of miR-152 was observed to cause a decrease in cell growth in Hela cells. In neuroblastoma samples, the expression of miR-152 was upregulated, and miR-152 negatively controlled apoptosis by downregulating pro-apoptotic genes such as conserved helix-loop-helix ubiquitous kinase, cullin 5 and growth arrest and DNA-damage-inducible, alpha (37). By contrast, Zhou *et al* (9) reported that cell proliferation was remarkably inhibited by overexpression of miR-152 in ovarian cancer cells using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide assay. Therefore, whether miR-152 acts as a tumor suppressor gene remains controversial.

In previous studies, several miRNAs have been demonstrated to affect target genes that are involved in the control of cell proliferation and apoptosis (14-20). It has been well established that phosphatidylinositol-3 kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK)-mediated signaling pathways are two of the most predominant signaling pathways in human cancer, since they are involved in cell proliferation, survival and metabolism (38,39). In breast cancer, overexpression of miR-152 significantly inhibited cell proliferation, colony formation and tumor angiogenesis by targeting IGF-1R and IRS1, and suppressing their downstream AKT and MAPK signaling pathways (17). KLF4 is a transcription factor that functions either as a tumor suppressor gene or as an oncogene in different contexts, and



is critical for the control of essential cellular processes (40). In glioblastoma stem cells, miR-152 markedly inhibits cell proliferation, migration and invasion, and promotes cell apoptosis by targeting KLF4 (23). In addition, miR-152 could inhibit the expression of lectin, galactoside-binding, soluble, 3 by downregulating KLF4, thus attenuating the activation of the MAPK kinase 1/2 and PI3K signaling pathway (23). In non-small cell lung cancer (NSCLC), Su *et al* (22) demonstrated that restoration of miR-152 significantly reduced cell proliferation, colony formation, migration and invasion partially via targeting ADAM17 (also known as tumor necrosis factor- $\alpha$  converting enzyme), which releases a variety of membrane-tethered proteins, the majority of which are associated with pathological processes such as cancer and inflammation (21). Another report revealed that the ectopic overexpression of miR-152 markedly inhibited NSCLC cell proliferation, promoted apoptosis, and suppressed migration and invasion through targeting FGF2 (22). CD151, a transmembrane protein of the tetraspanin family, participated in the mediation of tumor growth and metastasis (41). miR-152 was previously observed to be able to suppress the proliferation and motility of gastric cancer cell lines by targeting CD151 (26). In addition, miR-152 is also able to target Wnt1 and MMP3 (27) to inhibit cell proliferation in liver cancer cells, thus reducing glioma cell invasion and angiogenesis, respectively. Taking together, these findings suggest that miR-152 may modulate a variety of cellular processes such as cell proliferation, apoptosis and tumorigenesis via the regulation of its target genes and the tumor suppressor role of miR-152 in human cancer.

## 5. miR-152 in immune response

During the last 20 years, miRNAs have emerged as key regulators of a wide range of biological processes, including cell proliferation, differentiation, development and apoptosis (3,4,7). Recent studies indicate that specific miRNAs are important in the immune system by modulating the development of immune cells and regulating the expression of genes that are critically involved in the immune response (42).

The innate immune system provides the first line of defence against infections and natural killer (NK) cells are critical mediators of the innate immune response (43). Human leucocyte antigen (HLA)-G is important in the cellular immune response, since it inhibits NK cell activity (44). miR-152 may downregulate the expression of HLA-G by directly targeting its 3'-UTR, leading to increased NK cell-mediated cytotoxicity (45). Dendritic cells (DCs) are professional antigen-presenting cells, which bridge the innate and adaptive immune responses (45). Calcium/calmodulin-dependent protein kinase IIa (CaMKIIa), a major downstream effector of calcium signaling, regulates the critical stages of maturation and antigen-presentation capacity of human DCs (46). miR-152 is capable of inhibiting lipopolysaccharide-induced upregulation of major histocompatibility complex II expression and DC-initiated antigen-specific CD4<sup>+</sup> T cell proliferation by targeting CaMKIIa (47). These findings suggest that miR-152 acts as a negative regulator in the immune system. Therefore, in addition to human cancer, miR-152 is also important in the innate immune response.

## 6. Therapeutic potential of miR-152 in cancer

Aberrant miRNA expression is a common feature of various types of human cancer, and miRNAs are crucial in the development of cancer (3,7). As a result, numerous studies have focused on miRNA-based therapeutics, some of which are undergoing clinical trials in cancer patients (15). Targeting miRNAs may be used to control the growth of cancer cells, and also to enhance the efficacy of other therapies, such as reducing the drug resistance of tumors (48).

Resistance of cancer cells to chemotherapeutics is a clinical obstacle in the treatment of cancer patients (49). Cisplatin is the first-line chemotherapy drug for multiple malignancies (50). Xiang *et al* (15) demonstrated that miR-152 was involved in resistance to cisplatin in ovarian cancer. The authors confirmed that overexpression of miR-152 increased cisplatin sensitivity of SKOV3/DDP and A2780/DDP cells by inhibiting cell proliferation and promoting cell apoptosis via direct suppression of DNMT1. Therefore, miR-152 may serve as a therapeutic target for overcoming cisplatin resistance in ovarian cancer. This application is also likely to be used as a potential epigenetic therapeutic target in other types of cancer.

## 7. Conclusion

miR-152 is well conserved in evolution and possesses an identical seed sequence in different species. miR-152 may repress multiple target genes, a number of which have been validated by experimental methods. miR-152 binds to the 3'-UTR of its target genes, which are associated with different signaling pathways, thus leading to reduced cell proliferation and pro-apoptosis. In addition, miR-152 is involved in tumorigenesis, cell migration and invasion. miR-152 is located in the intron 1 of the COPZ2 gene, and is surrounded by a CpG island. Hypermethylation of the CpG island of miR-152 has been described in certain type of human cancer, and it may account for the downregulation of miR-152. These findings support the tumor suppressor role of miR-152 in human cancer, and suggest that miR-152 may serve as a prognostic biomarker and a therapeutic target in cancer patients.

However, the role of miR-152 in the progression of human tumors remains to be fully understood, particularly the mechanisms by which miR-152 contributes to tumorigenesis by binding to different target genes in different types of cancer. Further investigation on the function of miR-152 may lead to novel diagnostic and therapeutic approaches for the treatment of human cancer.

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