Role of microRNA-150 in solid tumors (Review)

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Abstract. MicroRNAs (miRNAs) are a family of small endogenous noncoding RNAs and their altered expression has been associated with various cellular functions, including cell development, proliferation, differentiation, apoptosis, signal transduction, tumorigenesis and cancer progression. Accumulating evidence has indicated that miRNA (miR)-150 plays an essential regulatory role in normal hematopoiesis and tumorigenesis; therefore, miR-150 may be a potential biomarker and therapeutic target in the diagnosis and treatment of various malignancies. The aim of the present review was to summarize the current knowledge on the functions and regulatory mechanism of miR-150 as an oncogene or tumor suppressor gene in solid tumors. In addition, its potential application as a tumor biomarker, targeted therapeutic strategy and index of prognosis in various cancer types was investigated.

Contents

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1. Introduction

MicroRNAs (miRNAs) are a family of small endogenous noncoding RNAs with a length of ~22 nucleotides. These molecules are able to negatively regulate gene expression at the post-transcriptional level by binding to the 3'-untranslated region (3'-UTR) of target messenger RNA (mRNA), resulting in mRNA degradation and/or translational repression (1,2). Notably, one mRNA sequence can be targeted by multiple miRNAs, while one miRNA has multiple mRNA targets (3). Depending on specific target genes, including oncogenes and tumor suppressor genes, miRNAs regulate numerous cellular functions, including cell development, proliferation, differentiation, apoptosis, signal transduction, tumorigenesis and cancer progression (4,5). In addition, miRNAs are potential prognostic and diagnostic biomarkers, as well as therapeutic targets for the treatment of various neoplastic diseases (6,7). Circulating miRNAs were initially described in 2008, and since then, >79 miRNAs have been reported to be plasma or serum biomarkers of several tumors, including prostate, lung, breast, colon, ovarian, esophageal, melanoma and gastric cancer (8,9). As a hematopoietic cell-specific miRNA, miRNA-150 (miR-150) plays an important role in normal hematopoiesis and hematological malignancies (10). A large number of studies have indicated that the aberrant expression of miR-150 is closely associated with tumorigenesis, cancer development, malignant behavior and a curative effect by influencing oncogenes and/or tumor suppressor genes (11-13). In addition to hematological malignancies, miR-150 is involved in a variety of solid tumors, including breast, lung and gastric cancer.

The role of miR-150 in normal and malignant hematopoiesis has been summarized in detail in a review article by He *et al* (14). In the present review, the functions and regulatory mechanism of miR-150 as an oncogene or tumor suppressor gene in certain solid tumors were discussed. In addition, its potential application as a tumor biomarker, targeted therapeutic strategy and index of prognosis in these cancer types was investigated.

2. miR-150 and cancer

Increasing evidence has indicated that miRNAs are associated with the molecular mechanisms of various clinical diseases and can potentially regulate numerous aspects of cellular

biological progress (4,5). In addition, different tissues exhibit different expression patterns. Monticelli *et al* were the first to investigate the systematic miRNA gene profiling in hematopoietic cells, demonstrating that its profiling was different from non-hematopoietic cells (15). As an important hematopoietic cell-specific miRNA, miR-150 is mainly expressed in B-cells, T-cells and natural killer cells, and plays a critical role in the differentiation of numerous hematopoietic cell lineages, particularly in lymphocyte development and function (14,16). In addition, a recent study has identified that serum circulating miR-150 is a sensor of general lymphocyte activation and may serve as a biomarker of human lymphocyte activation in healthy and disease conditions (17). miR-150 has been previously reported to be differentially expressed in various hematopoietic cell lineages of a specific developmental stage or characteristically up- or downregulated in various types of hematopoietic malignancies, including leukemia, lymphoma and myelodysplastic syndrome (14). In chronic myeloid leukemia (CML), miR-150 has been demonstrated to be involved in the mechanism of apoptosis induced by cisplatin in the human CML cell line, K562 (18). Xie *et al* (18)demonstrated a negative correlation between the expression levels of miR-150 and p53 following treatment of K562 cells with cisplatin, indicating that cisplatin induced apoptosis in the K562 cells by inhibiting miR-150 expression, which then upregulated p53 expression. Therefore, miR-150 may serve as a novel, clinically-useful biomarker in myeloid leukemia diagnosis and may have a curative effect. In addition, miR-150 is significantly downregulated in the majority of acute myeloid leukemia (AML) cases, which is not associated with the DNA copy number changes, methylation or mutations (11). Furthermore, the results of a recent study revealed that the plasma expression of miR-150 was significantly downregulated in AML patients at diagnosis when compared with healthy controls; however, miR-150 plasma expression in complete remission AML patients resembled that of the healthy controls (19). Receiver operating characteristic curve analyses revealed that plasma miR-150 may serve as a valuable biomarker for the differentiation of AML patients from control individuals, with a sensitivity and specificity of 80 and 70%, respectively (19). The expression signature of miR-150 in the plasma indicated that it may serve as a valuable diagnostic and potentially prognostic biomarker for human AML (19). Furthermore, in cutaneous T-cell lymphoma, upregulation of miR-150 inhibited tumor invasion and metastasis by targeting the chemokine CCL20 receptor, CCR6 (20). These results have provided a novel insight into the function of miR-150 as a tumor suppressor in the pathogenesis of hematological malignancies, as well as a basis for novel therapies targeting miR-150 for the treatment of these hematological malignancies discussed above.

In hematological malignancies, miR-150 dysregulation has been also demonstrated to be involved in the tumorigenesis and development of a number of solid tumors, as well as function as a biomarker of clinical diagnosis, outcome and prognosis of these solid cancer types(Table I and Fig. 1).

3. miR-150 in pancreatic cancer

Mucins (MUCs) are a family of high molecular weight glycoproteins, which are widely expressed in epithelial cells. Under normal physiological conditions, MUCs have a protective role on the adjoining epithelial tissues, whereas carcinomas and neoplastic lesions are often associated with an altered expression of MUCs (21). MUC4 is a specifically and restrictedly upregulated membrane-bound glycoprotein in pancreatic tumors and its potential role as a marker for pancreatic adenocarcinoma has been identified (22). In addition, a number of studies have indicated that the silencing of MUC4 expression resulted in altered tumor cell phenotypic characteristics (adhesion, aggregation and motility), decreased growth and a marked reduction in metastatic incidences in an orthotopic mouse model of pancreatic cancer (21). Furthermore, MUC4 overexpression potentiated pancreatic tumor cell proliferation, survival and invasive properties by stabilizing fibroblast growth factor receptor 1 through N-cadherin upregulation (Fig. 1). This supports the aforementioned observations and indicates the important role of the MUC4 in pancreatic adenocarcinoma development and progression (21,23,24). A recent study has demonstrated the presence of a highly conserved miR-150 binding site at the 3'-UTR of MUC4 and that its direct interaction with miR-150 downregulated the endogenous MUC4 protein expression levels, as shown in Table I (25). In addition, miR-150 overexpression inhibited the malignant behavior and enhanced the homotypic interactions of pancreatic cancer (25). Therefore, as a novel tumor suppressor miRNA, restoring the miR-150 expression levels may have a therapeutic effect in pancreatic cancer.

4. miR-150 in esophageal cancer

miR-150 expression has also been demonstrated to be significantly lower in esophageal squamous cell carcinoma compared with the normal esophageal mucosa levels (26). In addition, its deregulation contributed to a number of malignant characteristics, including cancer progression, higher clinical staging and poor prognosis (26). Zinc-finger E-box binding homeobox 1 (ZEB1), a crucial epithelial-mesenchymal transition (EMT)-inducer, may promote tumor invasion and migration through E-cadherin gene silencing in cancer (27-29). A recent study has indicated that, through the targeted-degradation of ZEB1, miR-150 induced mesenchymal-epithelial transition-like changes and evidently inhibited tumorigenicity and tumor proliferation (Fig. 1) (26). These results clarified the EMT-regulatory ability and clinicopathological significance of miR-150, and provided new insights into the prevention of metastasis and a promising novel candidate for targeted therapeutic strategies in esophageal cancer.

5. miR-150 in colorectal cancer

A recent study identified that the expression levels of miR-150 were downregulated in primary colorectal cancer and metastasis compared with the normal mucosa levels, while the expression was almost stably maintained in the subsequent primary tumor-to-metastasis transition (30). In addition, its expression gradually decreased during the tumor development, and patients with lower miR-150 expression levels in the tissues exhibited lower survival rates and reduced response to adjuvant chemotherapy, which was independent of other clinical risk factors associated with the clinical outcome (31,32). These observations suggested that miR-150 should be

considered as a potential biomarker associated with the prognosis and therapeutic outcome of colorectal cancer. However, the serum exosomal expression of miR-150 was significantly higher in primary colorectal cancer patients compared with healthy controls and significantly downregulated following surgical resection of the tumors (33). miRNA was also found to be secreted at significantly higher levels in colon cancer cell lines compared with the levels in a normal colon-derived cell line (33). The true positive rate of miR-150 for identification of colorectal cancer was 55.7%, while low false positive rates were observed for identification of the healthy controls (33). By contrast, the sensitivities of the carcinoembryonic antigen and carbohydrate antigen 19-9, which are known as biomarkers of colorectal cancer, were 30.7 and 16.0%, respectively (33). The exosomal miR-150 expression appeared to mirror pathological changes of colorectal cancer patients; therefore, it may be a promising biomarker for non-invasive diagnosis of the disease (Table I).

6. miR-150 in gastric cancer

In contrast to the low miR-150 expression in esophageal squamous cell carcinoma, high expression levels have been identified in gastric, breast and endometrial cancer tissues (34-37). In gastric cancer, miR-150 overexpression specifically repressed the expression of the pro-apoptotic gene, early growth response factor 2, at the translational level, as a result of promoting proliferation and growth of gastric cancer (38). The higher expression level of miR-150 in undifferentiated gastric cancer was associated with shorter postoperative patient survival; however, it was not a significantly independent prognostic factor in undifferentiated gastric cancer patients (35).

7. miR-150 in breast cancer

Huang *et al* revealed that blocking the action of miR-150 with inhibitors in breast cancer cell lines resulted in cell death, while ectopic expression of miR-150 promoted growth and clonogenicity, and reduced apoptosis (37). In addition, these authors identified that low levels of P2X7 receptor, an adenosine triphosphate-gated cation channel inducing apoptosis by leading Ca^{2+} release, were linked to the development of breast cancer (37). Furthermore,as shown in Table I, the 3'-UTR of P2X7 receptor contains a highly conserved miR-150-binding motif and directly interacts with miR-150, downregulating endogenous P2X7 protein levels and promoting breast cancer growth and malignant behaviors (37), which is consistent with the results of a previous study (36). These observations provided further understanding of the anti-apoptosis and growth-regulation role of miR-150 in the development of malignancies; therefore, targeting miR-150 may provide a potential therapeutic strategy for blocking proliferation in certain solid cancer types.

8. miR-150 in lung cancer

In previous studies, researchers identified that inhibition of miR-150 expression effectively delayed cell proliferation and promoted apoptosis in the lung carcinoma cells, A549, and was accompanied by increased p53 protein expression, which has a specific miR-150 binding site (39-41). Antisense oligonucleotide specific to miR-150 increased the chemotherapeutic sensitivity of A549 cells to anticancer drugs, which was promising for lung cancer therapy (40,41). In addition, miR-150 was aberrantly upregulated in non-small cell lung cancer (NSCLC) and promoted the growth of cancer cells through specifically targeting the 3'-UTR of p53 (42). These results indicated that miR-150 may promote lung cancer tumorigenesis by targeting p53. Overexpression of p53 promoted the expression of miRNAs, including miR-34a, miR-184, miR-181a and miR-148, which affected cell cycle progression in NSCLC tumorigenesis (43). These findings indicated that miR-150, p53 protein and relevant miRNAs comprised a complicated regulatory network in NSCLC tumorigenesis. In addition, miR-150 was found to be significantly upregulated in lung cancer clinical specimens, while sarcoma gene (SRC) kinase signalling inhibitor 1 (SRCIN1), which is an important regulator of SRC activity, was identified as a direct target of miR-150 (44). Therefore, the repression of SRCIN1 by miR-150 triggered the activation of the Src/focal adhesion kinase and Src/Ras/extracellular signal-regulated kinase signaling pathways, which eventually promoted the proliferation and migration of lung cancer cells (Fig. 1); this promotion by miR-150 cannot be reversed by the overexpression of SRCIN1 (44). Furthermore, miR-150 functioned as an oncogene by directly targeting human BRI1-associated receptor kinase 1 (BAK1) in NSCLC cells (45). These observations highlighted a novel molecular interaction between miR-150 and BAK1, and provided a novel strategy for NSCLC therapy through the downregulation of miR-150 expression. However, the underlying regulatory mechanism of miR-150 in NSCLC was controversial (46). A recent study demonstrated that miR-150 expression in peripheral blood mononuclear cells was significantly higher in lung adenocarcinoma patients compared with lung squamous cell carcinoma patients (47). This finding indicated that miR-150 may be a potential noninvasive molecular biomarker for the identification of histological subtypes of NSCLC and may assist the selection of effective therapeutic strategies to improve the treatment outcome.

However, in small cell lung cancer (SCLC), the expression levels of miR-150 were much lower in the tumor samples compared with normal lung samples (48). The miR-150/miR-886-3p signature, which may be used as an independent predictor of survival, was significantly correlated with the overall survival and progression-free survival of SCLC patients (48). Therefore, miR-150 may predict cancer progression and survival in early-stage SCLC patients and may be a promising prognostic biomarker and potential therapeutic targets in SCLC patients. However, the precise target of the miR-150 and the mechanisms underlying its involvement in tumor formation and prognosis in small cell lung cancer remain to be elucidated.

9. miR-150 in liver cancer

miR-150 was found to be significantly downregulated in hepatocellular carcinomas and may be a suitable candidate in the differentiation between tumoral and normal human primary hepatocytes (49). Zhang *et al* compared the miRNA profiles of $CD133^+$ and $CD133^-$ primary hepatocellular carcinoma subpopulations and identified upregu-

Table I. Level, targets and functions of miR-150 in solid tumors.

Type of cancer	Level	Targets	Functions
Pancreatic cancer	↓	MUC4	Overexpression of miR-150 inhibits growth, clonogenicity and invasion, as well as enhances intercellular adhesion in pancreatic cancer cells by downregulating MUC4.
Esophageal squamous cell carcinoma	↓	ZEB1	Through targeted-degradation of ZEB1, miR-150 induces MET-like changes and evidently inhibits tumorigenicity and tumor proliferation.
Colorectal cancer	↓	-	Exosomal miR-150 expression appears to mirror pathological changes in colorectal cancer patients and is a promising biomarker for non-invasive diagnosis of the disease.
Gastric cancer	↑	EGR2	In gastric cancer, forced miR-150 specifically represses the expression of pro-apoptotic gene, EGR2, at the translational level, as a result of promoting proliferation and growth of gastric cancer.
Breast cancer	↑	P2X7	The anti-apoptosis and maintain-growth role of miR-150 for the development of breast cancer was induced directly by downregulating P2X7.
Non-small cell lung cancer	↑	SRCIN1, P53, BAK1	miR-150 promotes the proliferation and migration of lung cancer cells through specifically targeting the 3'-UTR of p53, SRCIN1 and BAK1.
Liver cancer	↓	c-Myb	miR-150 may be involved in maintenance of the $CD133^+$ liver cancer stem cell phenotype through the negative regulation of the downstream target, c-Myb.

miR-150, microRNA-150; MUC4, mucin-4; ZEB1, zinc-finger E-box binding homeobox 1; EGR2, early growth response factor 2; SRCIN1, sarcoma gene kinase signalling inhibitor 1; BAK1, BRI1-associated receptor kinase 1.

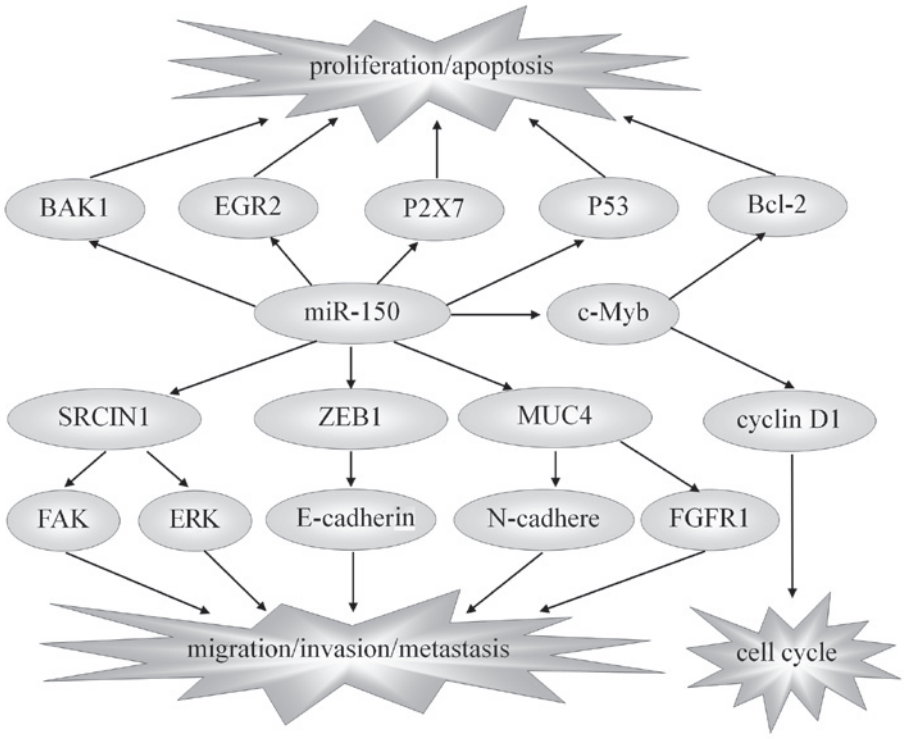

Figure 1. miR-150 and target genes in solid tumors. The reported direct targets of miR-150 include EGR2, P2X7, P53, c-Myb, SRCIN1, ZEB1, MUC4 and BAK1. Though regulating these target genes, miR-150 influences the proliferation, apoptosis, metastasis and prognosis of solid tumors, thus playing the role of anti-tumor or carcinogenesis. miR-150, microRNA-150; EGR2, early growth response factor 2; SRCIN1, sarcoma gene kinase signalling inhibitor 1; ZEB1, zinc-finger E-box binding homeobox 1; MUC4, mucin 4; BAK1, BRI1-associated receptor kinase 1; Bcl-2, B-cell lymphoma 2; FAK, focal adhesion kinase; ERK, extracellular signal-regulated kinase.

lation of miR-150 expression in $CD133^-$ subpopulations (50). In addition, overexpression of miR-150 resulted in a significant reduction of $CD133^+$ cells, along with significant inhibition of cell growth and tumorsphere formation (50). The levels of the cell cycle regulator, cyclin D1, and cell survival regulator, B-cell lymphoma-2, decreased in cells transfected with miR-150, which was consistent with the outcome of cell cycle arrest and cell apoptosis, as shown in Fig. 1 (50). Furthermore, these authors demonstrated that miR-150 may be involved in the maintenance of the $CD133^+$ liver cancer stem cell phenotype through the direct negative regulation of the downstream target, c-Myb, and its potential function in liver cancer stem cells may provide a novel therapeutic approach for hepatocellular carcinomas (50).

10. Conclusions

miRNAs have received increasing attention since their discovery, and one study has indicated that miRNAs regulate various cellular biological processes, as well as participate in the pathogenesis of diseases, particularly cancer (51). In addition, the circulating miRNA levels are useful in the diagnosis or evaluation of activity in human diseases (51).

In the present review, the critical role of miR-150 as an oncogene or tumor suppressor gene in relevant solid tumors was investigated, as well as its potential as a tumor biomarker, targeted therapeutic strategy and index of prognosis in different cancer types. In the aforementioned cancer types, certain relatively definite conclusions have been reached on the mechanisms underlying the role of miR-150 as an oncogene or cancer suppressor gene in the pathogenesis of tumors. However, in other cancer types, including osteosarcoma, Ewing sarcoma, hepatoblastoma and adrenocorticotropic hormone-secreting pituitary tumor, the regulatory mechanisms of miR-150 are unclear (52-56). In addition, it is unclear why miR-150 functions both as an onco-microRNA and a tumor suppressor microRNA in solid tumors. This may depend on factors including the pathological type, histological origin, cellular microenvironment and localization of the respective neoplasm.

The miR-150 expression regulation provides a promising novel candidate used as a tumor biomarker, targeted therapeutic strategy and index of prognosis in cancer. However, the use of circulating miRNAs as clinical biomarkers may face certain technical challenges. For instance, dilution effects in blood may limit the amount of RNA per volume of starting material, while cellular detritus and hemolysis may potentially impact reproducibility and sensitivity (17). Several studies have recently attempted to use miRNAs in the serum or plasma as a highly sensitive and non-invasive diagnostic or prognostic biomarker of various cancer types (17,33). However, currently, no collective view exists on which miRNA should be selected as a marker. At present, the role and mechanisms of miR-150 are not fully understood; however, future studies will aim to elucidate the existing controversial findings.

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