# miR-126: A novel regulator in colon cancer (Review)

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Abstract. Colon cancer is one of the most common, lethal diseases worldwide. Tumor metastasis and chemotherapy resistance are the main reasons for its poor prognosis and high fatality rate. Tumor development is thought of as one of the most complex cellular events as it is a multi-step cascading process involving infinite proliferation, invasion and immigration. Recently, increasing studies have demonstrated that microRNA-126 (miR-126) has an important role in colon cancer. The expression of miR-126 decreased significantly in colon cancer, particularly in highly metastatic cell lines. miR-126 controls tumor cell growth, metastasis and survival via inactivation of the oncogene signaling pathway, indicating that miR-126 may serve as a therapeutic target for anticancer therapy. Potentially, miR-126 was also reported to be an ideal molecular target as a novel biomarker for liver metastasis from colorectal cancer due to its changeable expression level. In the present review, the current knowledge regarding regulatory function of miR-126 is summarized along with its underlying mechanisms in colon cancer.

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### 1. Introduction

Globally, colorectal cancer (CRC) is one of the most lethal diseases. Synchronous liver metastases (SLM) account for ~15% of newly diagnosed CRC, which are often resistant to traditional treatment and develop into a poor prognosis (1). According to the National Cancer Institute, in 2012 CRC ranked as the fourth most common cancer type and the third most common cause of cancer-related mortality in the United States (2). Therefore, CRC is a large contributor to the cancer burden worldwide. The metastasis of CRC is the most common reason for treatment failure, and its complicated mechanism may include invasion and adhesion potential of tumor cells, epithelial-mesenchymal transition, extracellular matrix degradation, angiogenesis and chemotaxis of the tumor microenvironment. In addition, abnormal expression of microRNA (miR) is also one of the links.

miRs are a class of short, conserved, non-coding RNAs that modulate diverse biological processes by binding to the 3'-untranslated region (3'-UTR) of target mRNAs and affecting the post-transcription regulation of numerous genes (3-5). One of these, miR-126, encoded by intron 7 of the egfl7 gene (6), has been demonstrated to be significantly involved in angiogenesis, vascular integrity and various human diseases (7,8). Increasing data showed that miR-126 appears to inhibit tumor development by targeting multiple well-known genes, such as IRS (9), CXCR4 (10) and ADAM9 (11). Downregulation of miR-126 has an important role in tumorigenesis (12,13), tumor metastasis and invasion (10,14) by regulating a signaling pathway, which suggests a potential application of miR-126 in the treatment of cancer. Furthermore, miR-126 also has significant clinical influences as a novel biomarker for acute myocardial infarction (15), liver metastasis from CRC (16) and type 2 diabetes mellitus (17).

Recently, a number of studies have revealed that miR-126 is relevant to the tumor regulatory mechanism in the colon by aberrant activation or inactivation of signaling pathways. In the present review, an updated overview regarding the functions of miR-126 in colon cancer is reported.

# 2. miR-126 is associated with the activities of pomegranate polyphenolics in the colon

Due to the low survival rate of colon cancer, it is important to identify nutritional prevention approaches and their possible functional mechanism (18,19). Progress of precancerous lesions, particularly aberrant crypt foci (ACF), is found in human and animal colon cancer models and is critically implicated in carcinogenesis (20,21). Numerous studies (20-22) have indicated that chronic inflammatory markers, such as cyclooxygenase-2 and inducible nitric oxide synthase, are upregulated in chemically induced CRC patients and mice. However, natural polyphenol-enriched foods, such as pomegranate, have been reported to protect against colonic inflammation and colon cancer by negatively regulating inflammatory cell signaling in colon cancer cells (23-28). Banerjee et al (29) have demonstrated that in colon cancer, miR-126/vascular cell adhesion molecule-1 (VCAM-1) and miR-126/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)-mammalian target of rapamycin (mTOR) are highly correlated to the anti-inflammatory, cytotoxic, anticarcinogenic and therapeutic activities of pomegranate in vivo and in vitro. The underlying mechanisms may be that miR-126, activated by pomegranate polyphenolics, could correspondingly reduce VCAM-1, PI3K and AKT mRNA and protein expression in azoxymethane-induced colorectal ACF and inflammation. Specifically, miR-126 directly targets the regulatory p85 $\beta$  subunit of PI3K (12) and the PI3K/AKT pathway has been shown to have an important role in the cell survival mechanism and carcinogenesis in colon cancer through phosphorylation of downstream effectors, such as nuclear factor-kB (NF-kB) and mTOR (12,18,30,31). miR-126 can also bind to the 3'-UTR of VCAM-1, one of the cell adhesion molecules, to inhibit its expression, which contributes to colon cancer development, including carcinogenic transformation, angiogenesis and metastasis of cancer cells (32,33).

# 3. miR-126 regulates proliferation, migration and invasion of colon cancer

A number of studies have shown that miR-126 expression is significantly reduced in colon cancer tissues, particularly in highly metastatic cell lines (9,10,12,34-36). In 2013, Li et al (10) identified that miR-126 could suppress CRC cell viability, migration and invasion capacity by binding to CXCR4 3'-UTR. However, miR-126 could lead to the negative regulation of CXCR4 transcriptional activity and expression, resulting in a reduced number of migrating cells. The potential underlying mechanisms may be that the ligand of CXCR4 is stromal-derived factor 1 (SDF-1) (37), and colon cancer cells with a high expression of CXCR4 are easily metastasized to hepatic tissue, which is identified as rich in SDF-1. The chemokine family CXCR4/SDF-1 axis is important to hepatic metastases of colon cancer (38), as it can activate the NF-ĸB pathway and upregulate matrix metalloproteinase (MMP)-2, MMP-9 and vascular endothelial growth factor, and enhance the nitric oxide concentration (39). The family can induce tumor cell invasion by invading through the vascular basement membrane, correlated with endothelial cell growth, angiogenesis, hematopoiesis and other processes involved in tumor migration and invasion (40). As miR-126 can target CXCR4 directly to decrease its expression, and earlier studies (41,42) have provided support for the hypothesis that CXCR4 inhibitors, such as AMD3100 or anti-CXCR4 antibody, could effectively inhibit colonic neoplasm metastasis, restoration of miR-126 may produce a new therapeutic approach in the treatment of colon cancer metastasis.

Another study demonstrated that miR-126 suppresses the RhoA/Rho-associated protein kinase (ROCK) signaling pathway to inhibit colon cancer cell growth and metastasis (36). The data indicated that miR-126 expression was much more limited in colon cancer cells with a high metastatic ability, while restored miR-126 expression inhibited their cell-cycle progression, growth and invasion. RhoA expression is consistent with the results of a functional study on miR-126. Specifically, miR-126 can downregulate Rho/Rac guanine nucleotide exchange factor 2 and upregulate Rho GTPase-activating protein 5, followed by inactivation of Rho GTPase and the Rho GTPase signaling pathway, to exert its tumor suppressor role in colon cancer cells (36). A previous study suggested that RhoA, one of the Rho GTPases, has a critical role in cellular homeostasis, including cell division, motility, cell adhesion, phagocytosis and transcriptional regulation (43). A high level of RhoA promotes the plasticity of tumor cells, breaks the formation of adheren junctions and increases cell motility, causing cells to separate from the cancer, invade surrounding tissues, and metastasize to distant organs eventually (43-45). ROCK, the main RhoA downstream target, was also decreased owing to restoration of miR-126 expression, and the RhoA/ROCK pathway is closely associated with  $G_0/G_1$  cell cycle arrest (46). Collective studies have suggested that miR-126 could function as an inhibitor in colon cancer progression and miR-126/RhoA/ROCK may be a novel signaling target for developing potential therapeutic strategies.

# 4. miR-126 may serve as a novel biomarker for liver metastasis from colorectal cancer

Due to the relative stability in the circulation, miRs have been identified as potential serum markers for human diseases, including cancer (47). One of these, miR-126, is identified as an important metastasis-associated biomarker, and its level in metastatic CRC is significantly different from localized CRC (16). More specifically, previous data has shown that miR-126 is clearly correlated with development of CRC liver metastasis, and its expression is much lower in SLM CRC compared with localized CRC. Thus, serum miR-126 may be proposed as a novel signature for earlier detection of colorectal liver metastasis or clinical diagnosis of early-stage liver metastasis from CRC.

# 5. miR-126 improves the sensitivity of colon cancer cells to chemotherapy drugs

For colon cancer patients, chemotherapy resistance is another common cause of fatality. To the best of our knowledge, a decreased level of miR-126 is significantly observed in patients with a poor prognosis. However, upregulation of miR-126 can accelerate cell apoptosis, suppress colon cancer growth and invasion by targeting the *IRS1*, *SLC7A5* and TOM1 genes, and it was able to improve the sensitivity of colon cancer cells to chemotherapy drugs such as oxaliplatin (9). Oxaliplatin is often used for treating metastatic CRC. Of note, when colonic cancer cells are treated with different levels of oxaliplatin, activities of the cancer cells in the miR-126-inhibited group are all significantly higher compared with the miR-126 normal group, suggesting that downregulated miR-126 can decrease the sensitivity of colon cancer cells to chemotherapy drugs (9). As overexpressed miR-126 can reduce chemotherapy drug resistance of tumor cells, it may provide a beneficial therapeutic strategy against CRC.

### 6. Conclusion

In the present study, we conclude that downregulated miR-126 may be involved in the development and progression of colon cancer through three types of mechanisms. Firstly, it may stimulate tumor growth. Secondly, it was able to promote tumor metastasis. Thirdly, it could decrease the sensitivity of colon cancer cells to chemotherapy drugs, leading to a poor therapeutic effect. These findings not only highlight that miR-126 screening may offer early diagnosis regarding cancer progression and metastasis, but also facilitate novel therapeutic strategies against colon cancer by restoration of miR-126 expression. For colon cancer patients, examining the expression level of miR-126, which is vital for clinical treatment and prognosis, appears to be a rational approach.

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