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Killing two birds with one stone: miR-126 involvement in both cancer and atherosclerosis

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Abstract. – OBJECTIVE: Both cancer and atherosclerosis are the main causes of morbidity and mortality in the world, and some patients even suffer from both of them. Several studies have shown an association between the pathogenesis of cancer and atherosclerosis. It has been reported that miR-126 may participate in the pathological process of cancer and atherosclerosis. Therefore, we aimed to summarize the role of miR-126 in cancer and atherosclerosis respectively, as well as a possible association between them.

MATERIALS AND METHODS: In this paper, "miR-126" and "microRNA-126" are used as the first group of keywords, "atheromatosis" and "atherosclerosis" are used as the second group of keywords, and "tumor" and "cancer" are used as the third group of keywords. In PubMed, the authors selected one of the first group and the second group of keywords to search the literature related to miR-126 and cancer, and one of the first group and the third group of keywords was selected to search the literature on miR-126 and atherosclerosis. All collected articles are from 2021 and before. Irrelevant, withdrawn and review articles were excluded, and the included literature was mainly in the recent five years.

RESULTS: After collection and summary, miR-126 is found involved in cell apoptosis, proliferation, angiogenesis, inflammation, and other processes in both cancer and atherosclerosis by negatively targeting PI3K, VEGF, VCAM-1, EGFL7, CXCL12-CXCR4 axis, and LRP6. Moreover, we briefly review the prospects of miR-126 as a biomarker for the diagnosis and treatment of cancer and atherosclerosis in clinical applications.

CONCLUSIONS: It has been demonstrated that miR-126 can influence cancer and atherosclerosis by affecting the same or different target genes. Therefore, it facilitates our understanding of the common prevention and treatment strategies of cancer and atherosclerosis by regulating the miR-126-target genes network.

Key Words:
MiR-126, Cancer, Atherosclerosis, Target genes.

Introduction

Currently, cancer and atherosclerosis are seriously threatening human health, especially for the middle-aged and the elderly, whose mortality rates are on the rise[1,2]. However, the pathogenesis of cancer and atherosclerosis has not been fully explained, affecting their diagnosis and treatment. Humans are diagnosed and treated with cancer in their advanced years, during which atherosclerosis is highly prevalent[3]. As a result, some patients suffer from both atherosclerosis and cancer at the same time. Further studies have found that cell proliferation and apoptosis, angiogenesis, inflammation, and so on are also involved in cancer and atherosclerosis[4], which suggests a potential association between of them. Are there potential common regulatory mechanisms and therapeutic targets for these pathological and pathophysiological changes?

MicroRNAs (miRNAs) are highly conserved small non-coding RNAs with a length of about 22 nT[5]. Despite accounting for only 1-5% of the human genome, miRNAs can negatively regulate the expression of at least 30% of protein-coding genes by degrading or inhibiting mRNA translation[6]. MiRNAs play an important regulatory role in the progression of cell proliferation, apoptosis, differentiation, migration, and inflammation[7], which is involved in the pathophysiological mechanisms of both cancer and atherosclerosis[8]. Recently, the role of miRNAs in cancer progression and metastasis has been continuously clarified[9]. Simultaneously, evidence also shows that miRNAs regulate the initiation, development, and prognosis of atherosclerosis[10]. MiR-126, as an endothelial-specific miRNA, is thought to be involved in several diseases, such as diabetes[11,12], Parkinson's disease[13], viral myocarditis[14], and ischemic stroke[15]. MiR-126 may attenuate diabe-

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tes[11,12], Parkinson's disease[13], and ischemic stroke progression[15], while increasing the risk of viral myocarditis[14]. Besides the diseases mentioned above, miR-126 is considered closely related to cancer and atherosclerosis. MiR-126 is downregulated in malignant cancer cells such as endocrine glands cancer[16], reproductive system cancer[17], digestive system cancer[18], and respiratory system cancer[19]; interestingly, miR-126 is also down-regulated in most atherosclerotic patients, as well as animal and cell models of atherosclerosis[20], suggesting that miR-126 has a dual role in anti-cancer and anti-atherosclerosis.

MiR-126 was first discovered in the mouse (*Mus musculus*) heart by sequencing in 2002[21]. Langraf[22] found that miR-126 is tissue-specifically expressed in the hematopoietic system, respiratory system, digestive system, and reproductive system, especially in the cardiovascular system. Harris et al[23] found that miR-126 is highly expressed in endothelium-rich lung and heart tissues, primary cultured endothelial cells, but not in vascular smooth muscle cells and leukocyte cell lines. MiR-126 is encoded by the intron of epidermal growth factor-like domain 7 (EGFL7) genes[24], which is almost entirely expressed by endothelial cells. Based on the phenomenon above, miR-126 is almost completely derived from endothelial cells. Pre-miR-126 is processed into two mature subtypes, miR-126-3p and miR-126-5p, both of which are abundant in endothelial cells. MiR-126 regulates the expression of many different target genes, and its target genes are also regulated by a variety of miRNAs, which determines the diversity and complexity of the role of miR-126 in different diseases[25]. Therefore, although miR-126 is generally down-regulated in atherosclerosis and various cancers, its role may have both similarities and differences. The key lies in the difference between the diseased tissue microenvironment and its downstream targets. Both cancer and atherosclerosis belong to complex diseases that share some pathophysiological mechanisms[4]. The multiple targets of miR-126 may better explain the mechanistic basis behind the common mechanism of cancer and atherosclerosis. So, it is necessary to review and pool the available literature on this topic.

This review summarizes the relevant literature in recent years, emphasizes the role of miR-126 in cancer and the target genes of intervention, and tries correlating these with the targets and functions of miR-126 in the cardiovascular system. Understanding the role of miR-126 in cancer may help us understand its key function in cells of the cardiovascular system, to explore the common prevention and treatment targets.

MiR-126 in the Pathogenesis of Cancer

Cancer originates from normal cells and is the result of cumulative mutations in genes responsible for growth and differentiation. Compared with the normal tissue cells of its origin, cancer has the following characteristics: 1) Uncontrollable growth, indefinite proliferation (continuous division); 2) Local infiltration and distant metastatic spread. Studies found that there are miRNAs disorders in cancer, among which miR-126 is down-regulated in a variety of cancers, such as non-small cell lung cancer[19,26] breast cancer[27], liver cancer[28], esophageal cancer[29], colorectal cancer[30] and prostate cancer[25]. Further studies found that miR-126 can act as a cancer suppressor[31,32] by negatively regulating target genes, including PI3K, VEGF, VCAM-1, EGFL7, and LRP6, inhibiting cancer growth and metastasis in multistep that is closely related to their prognosis.

MiR-126 Inhibits Cancer Progression by Targeting PI3K

PI3K is composed of the regulatory subunit (p85) encoded by PIK3R2 and the catalytic subunit (p110) encoded by PIK3CA[33], which is an intracellular phosphatidylinositol kinase. PI3K can be activated by various mitotic signals and is related to oncogene products, such as v.src and v.ras[34]. Recent studies found that miR-126 is down-regulated and PIK3R2 is up-regulated in human non-small cell lung cancer A549 cell line[26] and prostate cancer tissue[25], and miR-126 and PIK3R2 are inversely correlated. Similarly, normal expression of miR-126 in the colon can negatively regulate the regulatory subunit p85β of PI3K, thus maintaining it at a low level, while miR-126 deletion in colon carcinogenesis reduces the targeted inhibition of p85β and boosting PI3K signaling[35].

Dual-Luciferase reporter results confirm that PIK3R2 is a direct target of miR-126, which negatively regulates the expression of the p85-regulatory subunit of PI3K in various cancer cell lines, such as non-small cell lung cancer cell line A549[26], human esophageal cancer cell line EC109[18], liver cancer Hep-G2 and BEL-7402 cell line[28], colorectal cancer cell line LS174T and DLD[35], breast can-

cer SKBR3/TR[36] and prostate cancer cell line[25]. Transcriptomics analysis also unraveled that miR-126 can target PIK3CA, the gene encoding the catalytic subunit p110 of PI3K[37]. Growth factor signal PI3K, plays a crucial role in cell proliferation, survival, metabolism, and apoptosis[33], which involves cancer initiation and development, such as apoptosis and proliferation of cancer cells, metastasis and invasion, angiogenesis and drug resistance.

MiR-126/PI3K and Cancer Apoptosis and Proliferation

Apoptosis can inhibit cancer growth, but cancer cells can escape from apoptosis through some mechanisms; excessive proliferation, even continuous proliferation, is a characteristic of cancer cell[38]. Consequently, insufficient apoptosis and excessive proliferation are both involved in cancer growth. Studies showed that miR-126 can inhibit cancer cell proliferation and induce apoptosis by targeting PIK3R2[17,18,25,26,39].

In vitro, miR-126 reduces cell viability of endometrial cancer RL95 and HEC1A cell lines, induces G1/S phase arrest as well as caspase-3-mediated apoptosis; *In vivo*, miR-126 induces regression of cervical cancer that depends on at least in part on PIK3R2 signaling[17]. Overexpression of miR-126-3p promotes apoptosis and inhibits the proliferation of cervical cancer HeLa cells via regulation of the PI3K/PDK1/Akt signaling pathway[39]. Similarly, up-regulation of miR-126 in non-small cell lung cancer A549 cell line can down-regulate PIK3R2, PI3K, and p-Akt protein, and then up-regulate the expression of cancer suppressor gene PTEN, which reduces the proliferation ability of cancer cells[26]. Further studies showed that miR-126 overexpression inhibited the proliferation of esophageal cancer cell line EC10917 and prostate cancer cell line, by negatively regulating target genes PIK3R2 and then PI3K/Akt signaling pathway[25]. In summary, miR-126 promotes cancer cell apoptosis, inhibiting proliferation by directly regulating PI3K and then its downstream signal Akt, effector molecules such as PTEN and caspase-3.

MiR-126/PI3K and Cancer Invasion and Migration

Local invasion and distant metastasis to other organs are hallmarks of malignancy. The activation of cancer invasion and migration ability is the key factor of cancer cell dissemination. Studies showed that miR-126 and its target gene PI3K are involved in the invasion and migration of some cancers[18,26,39-41].

Overexpression of miR-126 in esophageal cancer cell line EC109 inhibits cancer cell migration via negative regulating PIK3R2 and then PI3K/Akt signaling pathway[18]. Similarly, miR-126-3p overexpression by lentivirus-mediated transfection inhibits the migration of HeLa cells by regulating the PI3K/PDK1/Akt signaling pathway[39]. The anillin actin-binding protein (ANLN) highly expressed in various cancers, is closely related to cancer metastasis and overall short survival[42]. In three mRNA datasets from GEO, GSE18842, GSE19804, and GSE101929, it was found that ANLN was significantly up-regulated in human non-small cell lung cancer A549 cell line and was inversely correlated with miR-126[43]. Related studies confirmed that ANLN is regulated by PI3K/Akt signaling pathway[41], suggesting that miR-126 can regulate PI3K/Akt signaling and its downstream effector ANLN to inhibit lung cancer metastasis. Similarly, miR-126 also down-regulates PI3K/Akt signaling in non-small cell lung cancer A549 cell line, thereby up-regulating the expression of cancer suppressor gene PTEN, resulting in decreased migration and invasion[26]. Epithelial-mesenchymal transition (EMT) is considered the initial step of cancer metastasis. MiR-126 mimics-transfected lung cancer cell lines SPC-A1 and LLC showed an upregulation of p-PDK1 and p-Akt, and a downregulation of Snail and a pro-EMT transcription factor protein, thus EMT induced by TGF-β1 was inhibited[40]; Snail has been confirmed to be regulated by PI3K/Akt signaling[44], that suggests that miR-126 inhibits lung cancer EMT and metastasis by regulating PI3K/Akt/Snail signaling pathway. To sum up, miR-126 can inhibit cancer metastasis by targeting PI3K and its downstream signal Akt, PDK1, and effector molecules such as ANLN, PTEN, and Snail.

MiR-126/PI3K and Cancer Chemoresistance

Chemoresistance has become a major obstacle to cancer treatment and a main limiting factor for the cure of cancer patients[45]. MiR-126 can reduce the drug resistance of gastric cancer[46], breast cancer[47], and other cancers by targeting PI3K. Resistance to chemotherapy is closely related to the upregulation of multidrug resistance-associated protein (MRP)[46]. Studies found that miR-126 can inhibit PI3K/Akt/MRP1 pathway by targeting PIK3R2, thereby reducing the resistance of gastric cancer to cisplatin[46]. Overexpression of LncRNA HOTAIR weakens the effect of miR-126 on drug

resistance by the directly binding and inhibiting of miR-126 and then activating the PI3K/Akt/MRP1 pathway[46]. These results demonstrate that miR-126 attenuates cisplatin resistance by regulating the PI3K/Akt/MRP1 pathway.

Collectively, miR-126 plays an important role in inhibiting cancer apoptosis and proliferation, invasion, and metastasis, and reducing drug resistance. PIK3R2 is an important target gene for miR-126 in inhibiting cancer development by interfering with PI3K and its different downstream signal and effector molecules.

MiR-126 Inhibits Cancer Process by Targeting VEGF

Vascular endothelial growth factor (VEGF) is a highly specific vascular endothelial cell growth factor. The VEGF family includes VEGF-A—VEGF-E and placenta growth factor (PGF), of which VEGF-A is the most important, so VEGF is referred to as VEGF-A in general[48]. VEGFR1/2/3, three receptor tyrosine kinases, mediates the biological function of the VEGF family. Low expression of miR-126 was accompanied by high expression of VEGF in various cancer tissues[49,50]. Interestingly, the degree of VEGF overexpression is not the same in different types and stages of progression of the same cancer. For example, VEGF expression is higher in triple-negative breast cancer tissues than that in non-triple-negative breast cancer tissues, implying a close relationship to the occurrence, development, and prognosis of cancers[51]. Combining the results from both overexpression and inhibition experiments further revealed that VEGF is significantly inversely related to miR-126 in liver cancer[52], ovarian cancer[53], breast cancer[54], and gastric cancer[55]. In oral squamous cell carcinoma OSCC cell lines, the role of miR-126 is related to the regulation of VEGF-A, but not VEGF-C and VEGF-D[32]. The expression of VEGF-A is significantly down-regulated by exogenous miR-126 in some thyroid cancer cell lines[16]. MiR-126 inhibits the effect of VEGF-A and VEGFR-2 on lung cancer, which vanishes when miR-126-5p, an active form of miR-126, is inhibited[50], suggesting that VEGF is downregulated by miR-126.

Targeting VEGF-A by miR-126 was predicted by bioinformatics analysis in ovarian cancer[53] and gastric cancer[55]. The dual-luciferase reporter assay further confirmed that VEGF-A is a target gene of miR-126 in gastric cancer[55]. It is well known that VEGF is necessary for cancer angiogenesis, growth, and metastasis, suggesting that miR-126 is involved in pathological processes, such as apoptosis, proliferation, metastasis, invasion, and angiogenesis of cancer cells by targeting VEGF.

MiR-126/VEGF and Cancer Proliferation and Apoptosis

MiR-126 binds directly to VEGF and negatively regulates its expression, which is another important mechanism of miR-126 by inhibiting proliferation and promoting apoptosis in many cancers[50,56,57]. Down-regulation of miR-126 and up-regulation of VEGF-A and VEGFR-2 inhibit the apoptosis of NCI-H1299-human non-small cell lung cancer cell line; conversely, miR-126-5p overexpression inactivates VEGF-A and VEGFR-2/ERK signaling pathway and promotes apoptosis[50]. LV-miR-126 mimics induce cell cycle arresting in the G1 phase and down-regulates VEGF in ovarian cancer SKOV3 cell line[56]. LV-has-miR-126 inhibitor transfected ovarian cancer SKOV3 cell line showed upregulation of VEGF and increased number of S phase cells[56]. In summary, miR-126 affects the cell cycle, thus inhibiting the proliferation and promoting apoptosis of cancer cells by targeting and negatively regulating VEGF and its downstream signals.

MiR-126/VEGF and Cancer Invasion and Migration

VEGF overexpression promotes cancer angiogenesis and metastasis, and is involved in the invasion and migration of breast cancer[58], ovarian cancer[53], and non-small cell lung cancer[50]. As mentioned above, miR-126 can bind to and inhibit VEGF, suggesting that miR-126 is expected to inhibit cancer invasion and migration by targeting VEGF.

Studies found that low expression of miR-126 and high expression of VEGF in breast cancer are more prone to metastasis: ectopic expression of miR-126 led to a significant decrease in VEGF expression at 7 days and 14 days after surgery of the primary breast cancer in mice, inhibiting its lung metastasis[58]. At the same time, in NCI-H1299, a human non-small cell lung cancer cell line, miR-126 was down-regulated and its target gene, VEGF-A, and VEGFR-2 were up-regulated, which promoted cancer cell invasion[50].At the same time, the ectopic expression of VEGF-A can offset the cancer invasion induced by miR-126[53]. Similarly, LV-miR-126 mimics were found to inhibit cell invasion and down-regulate VEGF expression in the SKOV3-ovarian cancer cell line; while LV-has-miR-126 inhibitors have the oppo-

site effect[56]. In lung cancer cell lines, miR-126 inactivates VEGF-A/VEGFR-2/ERK signaling pathway, and then inhibits metastasis[50]. To sum up, the downregulation of miR-126 leads to abnormal accumulation of VEGF-A and activation of its downstream signals. In contrast, the up-regulation of miR-126 is expected to negatively regulate VEGF-A, thereby inhibiting cancer invasion and migration.

MiR-126/VEGF and Cancer Angiogenesis

Angiogenesis is necessary for cancer growth and progression. VEGF, as the most effective activator of angiogenesis, promotes cancer angiogenesis by binding to VEGF receptors on vascular endothelial cells[59]. Meanwhile, miR-126, specifically expressed in vascular endothelial cells, is also highly related to cancer angiogenesis. MiR-126 inhibits angiogenesis partly by targeting and negatively regulating VEGF in multiple cancers, such as oral squamous cell carcinoma[32], liver cancer[52], gastric cancer[55], and breast cancer[57].

In vivo studies found that microvessels density and VEGF-A expression were negatively correlated with miR-126 in gastric cancer tissue[55]. Experiments combining overexpression and inhibition of miR-126 found that miR-126 suppressed hepatocellular carcinoma growth by inhibiting VEGF expression and subsequent angiogenesis both *in vivo* and *in vitro*[52]. Upon being restored or inhibited by lentiviral transfection, miR-126 was confirmed to inhibit the growth and angiogenesis of gastric cancer by targeting VEGF-A and then regulating the activity of its downstream signals, such as Akt, mTOR, and ERK1/2 in gastric cancer cell lines SGC-7901, MKN-28 and MKN-45[55]. Transfection of miR-126 into breast cancer cell line MCF inhibits VEGF-A signaling pathway, reduces cancer angiogenesis, and delay its growth[57]. However, anti-VEGF monotherapy is not effective in improving the survival rate of breast cancer[57]. Resistance to VEGF inhibition may be due to the fact that angiogenic factors such as FGF-2 and IL-6 are upregulated to compensate for VEGF[60]. Therefore, it is speculated that miR-126 will have superior anticancer efficacy compared with VEGF inhibitors alone at similar concentrations since miR-126 has a multi-target anti-cancer effect besides targeting VEGF.

MiR-126/VCAM-1 and Cancer Progression

Vascular cell adhesion molecule-1 (VCAM-1), a member of the immunoglobulin superfamily, plays an important role in the immune surveillance of various diseases[61]. VCAM-1 is expressed at low levels in resting endothelial cells but increases dramatically on the luminal surface and intercellular interface of endothelial cell membrane under the strong induction of many factors, especially inflammatory factors[62]. VCAM-1 plays a key role in the inflammatory response by mediating leukocyte adhesion and rolling, as well as recruitment to the inflammatory site[62]. Interestingly, high expression of VCAM-1 was also detected in malignant cancers such as renal carcinoma[63], gastric carcinoma[64], colorectal carcinoma[65], prostate carcinoma[66], chondrosarcoma[67], and leukemia[68], suggesting a close relationship between VCAM-1 and cancer progression, especially cancer metastasis and angiogenesis[69]. Contrary to the high expression of VCAM-1, miR-126 is expressed at low levels in a variety of cancers. It was revealed that miR-126 and VCAM-1 were negatively correlated by overexpressing or inhibiting miR-126 in malignant cancers such as colon cancer[65], prostate cancer[66], and chondroma[67], and VCAM-1 was one of the target genes of miR-126. In a word, miR-126 can also target VCAM-1 to inhibit cancer metastasis and invasion, angiogenesis, and cancer-related inflammation.

MiR-126/VCAM-1 and Cancer Metastasis and Invasion

Cancer cells release cytokines, and their concurrent inflammation was activated, which promotes the up-regulation of VCAM-1[70]. Combined with animal model and clinical sample analysis, a group of 18 genes was identified as lung metastasis gene characteristics (LMS), among which VCAM-1 was listed[71], suggesting a strong relationship between VCAM-1 and cancer metastasis[61]. Similarly, the high expression of VCAM-1 in breast cancer contributes to its ability to metastasize to lungs. Further studies have found that up-regulation of VCAM-1 expression in mice can also promote lung metastasis of vaccinated cells, whereas antibodies against VCAM-1 can significantly reduce this metastasis rate[72]. Upon entering the blood stream, cancer cells will form platelet-cancer cell aggregates that can up-regulate the expression of VCAM-1 and easily get stuck in small blood vessels. Cancer cells were then closely combined with the walls of blood vessels by VCAM-1-mediated, which is a prerequisite for cancer metastasis[72]. Therefore, the region of VCAM-1 overexpression tended to present at the site of cancer cell adhesion and early aggregation in the circulation. Integrin alpha4 expressed by

cancer cells, such as melanoma cells, can interact with VCAM-1 of endothelial cells, triggering the activation of Rac1 (a Rho-like GTPase), leading to cytoskeletal rearrangement[73]. It is believed to remodel the tight junctions between vascular endothelial cells, thus promoting the transendothelial migration of cancer cells[73]. Direct evidence shows that miR-126 targets VCAM-1 and is involved in the metastasis and invasion of a variety of cancers, including prostate cancer[66], leukemia[68], and chondroma[67].

Most patients with advanced prostate cancer (PCa) will eventually develop bone metastases that lead to intractable pain[66]. Wnt-1-inducible secretory protein 1 (WISP-1) is a member of the homocysteine protein 61/connective tissue growth factor/nephroblastoma overexpressed gene family and is considered a factor promoting bone metastasis[74]. Osteoblasts transfected with WISP-1 shRNA can promote migration and VCAM-1 expression of human PCa cell lines PC3 and DU145 mediated by the osteogenic medium[66]. Osteogenic-derived WISP-1 inhibits miR-126 expression, while miR-126 mimics reverse WISP-1-promoted prostate cancer bone metastasis and VCAM-1 expression. Overall, miR-126/VCAM-1 is involved in WISP-1-induced prostate cancer bone metastasis[66]. Moreover, by co-culturing LAMA84-chronic myeloid leukemia cells with endothelial cells, it was found that miR-126 can shuttle in endothelial cells, negatively regulating the expression of VCAM-1, motility, and adhesion of LAMA84[68]. It is suggested that miR-126 inhibits the metastasis of leukemia by inhibiting VCAM-1 expression[68]. As a primary malignant cancer of bone, chondrosarcoma is prone to local invasion as well as distant metastasis, especially lung metastasis. Naringin can enhance miR-126 expression, reduce VCAM-1 expression, and inhibit movement and invasion of chondrosarcoma cells, while miR-126 inhibitor weakens the effects of Naringin. It is suggested that miR-126 may be involved in the migration and invasion of chondrosarcoma by down-regulating VCAM-1[67]. To sum up, targeting VCAM-1 is also one of the important mechanisms of miR-126 inhibiting cancer metastasis and invasion.

MiR-126/VCAM-1 and Cancer Angiogenesis

Studies have shown that VCAM-1 is highly related to cancer angiogenesis. Yong-Bin et al[69] reported that microvessel density in VCAM-1 positive cancer tissues was higher than that in VCAM-1 negative cancer tissues of gastric cancer. The interaction of α4β1 integrin, the main binding partner of VCAM-1, with the Ig-like domains 1 or 4 of VCAM-1 is critical for cancer angiogenesis[75].

Garmy-Susini firstly observed that VCAM-1 and α4β1 integrin were expressed on endothelial cells and vascular smooth muscle cells respectively in developing vessels of breast cancer, whereas anti-mouse VCAM-1 antibody (M/K-2) reduced microvessel formation in a mouse model[75]. Additional literature has shown that VCAM-1 antibody blocks IL-4/13-induced angiogenesis *in vitro*, while angiogenesis induction by IL-4 and IL-13 is also inhibited by anti-integrin α4 antibodies *in vivo*[76]. Recently, the Ig-like domain 6 of VCAM-1 (VCAM-1-D6) was identified as a potential angiogenesis target. Low expression of VCAM-1 induced by siRNA-mediated VCAM-1 knockdown was found to reduce TNF-α-induced HUVEC migration and angiogenesis. Competition assays showed that TNF-α-induced HUVEC tube formation was specifically inhibited by VCAM-1-D6 fused to Fc, but not by Fc alone, suggesting that VCAM-1-D6 is a critical domain for TNF-α-induced angiogenesis[77]. These data suggest that VCAM-1 may be a key target for the regulation of cancer angiogenesis. However, although a large piece of literature has confirmed that miR-126 negatively regulates VCAM-1 in cancers[78], the direct evidence that miR-126 inhibits cancer angiogenesis by negatively regulating VCAM-1 is obviously insufficient, and further research is needed.

MiR-126/VCAM-1 and Cancer-associated Inflammation

In recent years, cancer and inflammation have been found to be closely related, in which inflammatory cells act as a bridge[79]. There are a lot of macrophages around the cancer cells, called cancer-associated macrophages (TAM), which express VCAM-1 during differentiation[80].

Studies have shown that CCL18 secreted by TAMs promotes the malignant progression of pancreatic cancer and induces glycolytic phenotype transformation, partly due to induction of VCAM-1 paracrine. Conversely, VCAM-1 induces lactate production and enhances aerobic glycolysis in pancreatic cancer cells, activates macrophages, and makes them form a TAM-like phenotype. There is a positive feedback loop between VCAM-1 and TAM. Further study has confirmed that TAM promotes the progression of pancreatic ductal adenocarcinoma

and the Warburg effect by the CCL18/NF-κB/VCAM-1 pathway[81]. In addition, TAMs infiltration increased and VCAM-1 upregulated, cancer cell apoptosis decreased, and proliferation index increased in breast cancer after electronic cigarette exposure that affects breast cancer cell survival by modulating VCAM-1 and integrin α4β1 through direct interaction with infiltrating macrophages[82]. Other studies showed that VCAM-1 expression induced by IL-1β in glioblastoma may regulate the adhesion between glioblastoma and monocytes[83]. Therefore, VCAM-1 is closely related to cancer-related inflammatory factors and inflammatory cells[83]. As mentioned above, VCAM-1 is involved in cancer survival, proliferation, metastasis, and other pathological processes by affecting TAM. MiR-126 has been shown to target negative VCAM-1 in a variety of cancers, however, direct evidence that miR-126 affects cancer growth by targeting VCAM-1 in cancer-associated inflammation is insufficient.

MiR-126/EGFL7 and Cancer Progression

EGFL7 is a protein molecule containing an N-terminal signal peptide, a cysteine-rich EMI domain (named for its discovery in the EMIL protein family), and two epidermal growth factor-like domains[84], which belongs to the epidermal growth factor (EGF) -like protein family. EGFL7 is secreted specifically by endothelial cells[85] that is highly expressed in normal embryonic tissues, but barely expressed in mature tissues. Interestingly, EGFL7 is highly expressed in endothelial cells of cancer tissues[86], suggesting its importance in the occurrence and development of cancer. Although miR-126 expression is higher and EGFL7 is lower in hepatocellular carcinoma tissues (HCC) than that in normal tissues adjacent to HCC[87]; miR-126 also is found to increase the expression of EGFL7 in lung cancer-associated cell line A549[86], the expression of miR-126 was significantly low and the expression of EGFL7 was high in most cancers, indicating a suggestive inverse association between miR-126 and EGFL7[88-91]. Bioinformatics prediction further revealed that EGFL7 is a potential target of miR-126[86,92], which was confirmed by luciferase reports in ovarian cancer tissues[88]. More and more evidence showed that miR-126 plays a crucial role in cancer biology by negative regulation targeting EGFL7, participating in cancer cell proliferation, apoptosis, metastasis, invasion, and angiogenesis to affect the pathological process of cancers.

MiR-126/EGFL7 and Cancer Proliferation and Apoptosis

EGFL7, as a potential biomarker of malignancy, is overexpressed in colorectal cancer[93]. The transfection of EGFL7 siRNA significantly decreased the proliferation of SW620 and LoVo cells-colorectal cancer cell lines; at the same time, EGFL7 inhibits anoikis by regulating anoikis marker proteins, which is related to PI3K/Akt signaling pathway[94]. A large body of previous research shows that the effects of EGFL7 on proliferation and apoptosis are reversed by miR-126 in ovarian cancer[88], renal cell carcinoma[95], liver cancer[87], oral squamous cell carcinoma[96], and non-small cell lung cancer[86].

Overexpression of miR-126 inhibits EGFL7 in HCC cell lines (HepG2, Bet-7402, and smmc-7721), thereby inhibiting cell proliferation and inducing apoptosis[89]. By transplantation of HCC cell lines to establish nude liver cancer mice model, it was shown that enforced miR-126 expression decreased cancer weight 3 weeks after transplantation; once the expression of miR-126 was inhibited, less apoptosis and more proliferation were found[89]. A subsequent study found that miR-126 targets EGFL7 as its main molecular mechanism for down-regulating the ERK signaling pathway[89]. Cell proliferation correlation analysis showed that miR-126 targets EGFL7 to inhibit the proliferation of A549 cells *in vitro* and inhibit cancer growth *in vivo*[86]. To sum up, EGFL7 is one of the important targets for miR-126 to promote cancer cell apoptosis, inhibit proliferation, and ultimately suppress cancer growth.

MiR-126/EGFL7 and Cancer Migration and Invasion

EGFL7 and the β3 integrin, one of its receptors, signal axis is a key regulator in cancer metastasis[97]. EGFL7 is highly expressed in cancer tissues and serum of HCC patients, and its expression level is closely related to HCC cancer vein invasion[98]. Inhibition of EGFL7 expression can significantly inhibit the invasion and metastasis of HCC cells *in vivo* and *in vitro*, in part due to EGFR-mediated FAK phosphorylation and then changes in cancer cell migration capacity[98].

EGFL7 was upregulated in colorectal cancer cell lines, whereas transfection of EGFL7 siRNA significantly reduced the invasiveness of SW620 and LoVo colorectal cancer cell lines[94]. When EGFL7 is expressed in cancer cells, it promotes cancer immune evasion by activation of cancer blood vessels[99]. As mentioned above,

miR-126 down-regulation is an important reason for EGFL7 up-regulation, and miR-126 can target EGFL7 to delay the migration and invasion process of ovarian cancer[88] and renal cell carcinoma[95]. Low expression of miR-126 up-regulates the expression of EGFL7, resulting an invasive phenotype in ovarian cancer patients and poor prognosis; once restoring miR-126 expression can significantly inhibit the migration and invasion of cancer cells[88]. Similar results were obtained from a renal cell carcinoma mice model[95]. To sum up, miR-126 negative regulation of EGFL7 involves cancer metastasis and invasion in different cancers.

MiR-126/EGFL7 and Cancer Angiogenesis

The collective migration of endothelial cells is a critical step in angiogenic[100]. EGFL7 is an essential factor for the formation of the vascular lumen, which plays an important role in maintaining the spatial structure and migration direction of endothelial cells during migration. In the absence of EGFL7, lumen formation is blocked, affecting the improvement of vascular function, while overexpression of EGFL7 is prone to result in vascular dysplasia[95]. Studies have found that, in cancer-associated blood vessel wall, the basement membrane is missing or discontinuous, allowing cancerous tissue to pass through the wall of blood vessels and enter the bloodstream. These characteristics are related to the overexpression of EGFL7, which makes the endothelial cell motility too strong[95]. EGFL7 has recently been identified as an important regulator of angiogenesis and progression in renal cell carcinoma. The overexpression of miR-126 inhibits cancer angiogenesis, at least in part by targeting EGFL7[95].

Studies found that miR-126 mimics and siRNA-EGFL7 significantly reduced the size, weight, and microvessel density of liver cancer xenografts in nude mice[87]. The rat model of hepatoma was established by transplanting hepatoma cell lines (HepG2, Bet-7402, and smmc-7721), and it was found that overexpression of miR-126 in nude mice reduced cancer angiogenesis, while miR-126 inhibition promoted cancer angiogenesis[89]. Further study has found that miR-126 inhibits angiogenesis in hepatocellular carcinoma mainly by decreasing EGFL7 and then the ERK signaling pathway[89]. In a word, miR-126 can indirectly inhibit cancer growth and metastasis by targeting EGFL7, and thereby inhibiting angiogenesis in renal cell carcinoma and HCC.

MiR-126/CXCL12-CXCR4 axis and Cancer Progression

C-X-C motif chemokine ligand 12 (CXCL12), also known as stromal cell-derived factor-1 (SDF-1), is a homeostatic chemokine secreted mainly by fibroblasts, inflammatory, and endothelial cells[101,102]. C-X-C Motif Chemokine Receptor 4 (CXCR4) is widely expressed in hematopoietic cells, with CXCL12 as its sole ligand[103-105]. Their interaction forms a coupling molecular pair, the CXCL12-CXCR4 axis, which is closely related to cell signal transduction and migration[106]. Because of this, the CXCL12-CXCR4 axis may be involved in several aspects of cancer progression, including angiogenesis, metastasis, and survival. Interestingly, both CXCL12[107] and CXCR4[108] have been found to be the target genes of miR-126, suggesting that miR-126 inhibits cancer progression by targeting CXCL12 and /or CXCR4.

The miR-126/CXCL12-CXCR4 is responsible for inhibiting cancer cell metastasis. There was an increase in IL-6 in patients with inflammatory colorectal cancer, which was related to cancer size, stage, and metastasis[109]. It was found that miR-126 affected macrophages function, and subsequently inhibited the proliferation and migration of colon cancer cells through CXCL12 / IL-6[107]. Clinical studies showed a high level of CXCR4 and low level of miR-126 in the colorectal cancer tissues, which were related to distant metastasis, clinical TNM stage, and poor prognosis[110]. Similar results were shown *in vitro* and *in vivo*. For example, miR-126-3p reduced the metastasis of lung cancer *in vivo* and H460 lung cancer cells by targeting blocking CXCR4[19,111]. In addition, miR-126 also inhibited the invasion of colon cancer cell lines HCT116 and SW480 by CRCX4/RhoA[112], and the proliferation of cancer cells in gastric cancer[113], thyroid cancer[114], and colon cancer[112] by targeting CXCR4. As a consequence, the CXCL12-CXCR4 has become an attractive target of miR-126 for cancer therapies.

MiR-126/LRP6 and Cancer Progression

Lipoprotein receptor-related protein 6 (LRP6) is a co-receptor for Wnt signaling[115]. When Wnt binds to LRP6 and is phosphorylated, the canonical Wnt-β-catenin signaling pathway is triggered, which ultimately affects cell proliferation, survival, and differentiation[116]. The microenvironment of cancers is rich in the Wnt ligand family, and abnormal signal transduction of Wnt signaling has been observed in cancer cells. LRP6, as an indispensable co-receptor of Wnt, is overexpressed

in colorectal cancer, liver cancer, and breast cancer of epithelial origin[117]. Silencing LRP6 reduces Wnt signaling and inhibits cancer cell proliferation in breast cancer cells *in vitro*; consistent with the literature mentioned above, the LRP6 antagonist Mesd significantly inhibited the growth of MMTV-Wnt1 cancers *in vivo*[118]. It suggests that LRP6 is a potential therapeutic target for breast cancer, especially for Wnt-activated breast cancer subtypes. It is found that LRP6 is significantly up-regulated in liver cancer tissues and cell lines (HepG2, SMMC-7721, BEL-7402), and is negatively correlated with the expression of miR-126-3p[28]. And then LRP6 was identified as a negative target of miR-126-3p. MiR-126-3p significantly inhibits hepatoma cell migration and invasion of extracellular matrix gel, as well as preventing the formation of endothelial capillaries *in vitro*. Overexpression of miR-126-3p significantly reduced the cancer volume and microvessel density of hepatocellular carcinoma in nude mice[28]. Similarly silencing LRP6 and repairing miR-126-3p had the same effect. These results suggesting that the inhibitory effect of miR-126 on hepatocellular carcinoma metastasis and angiogenesis is closely related to LRP6[28]. To sum up, miR-126 was found to target PI3K, VEGF, VCAM-1, EGFL7, CXCL12-CXCR4 axis, and LRP6 in cancers, affecting the downstream signal and effector molecules, inhibit cancer apoptosis and proliferation, migration and invasion and angiogenesis, delay the process of cancer. However, a few contrary opinions suggest that further refinement and in-depth study is needed to fully understand the targeting effects of miR-126 and their impact on cancer.

MiR-126 in the Pathogenesis of Atherosclerosis

Atherosclerosis is the underlying pathological process of ischemic cardiovascular and cerebrovascular diseases, which is characterized by the formation of atheroma or fibrous plaque in the intima of large and medium arteries[119]. Consistent with cancers, miR-126 is down-regulated in most patients with cardiovascular disease and atherosclerosis, and overexpression of miR-126 is beneficial for most cardiovascular disease models[20]. Vascular endothelial cell apoptosis is an initial step of atherosclerosis, inflammatory response plays a crucial role in the whole progression, and intraplaque angiogenesis is involved in atherosclerotic plaque instability[120,121]. Interestingly, as in cancer, miR-126 regulates the above pathological processes in atherosclerosis by targeting PI3K, VEGF, VCAM-1, EGFL7, and LRP6 genes.

MiR-126/PIK3R2 and Endothelial Cell Apoptosis

Normal endothelial cells line the luminal surface of blood vessels, which effectively prevent atherosclerosis and its complications. On the contrary, apoptosis of endothelial cells facilitates atherogenesis and its thrombotic complications through multi-links: 1) Damage endothelial function, lead to immune and inflammatory disorders[122]; 2) Destroy the endothelial barrier function and then promote lipids deposition in the arteries intima[123]; 3) Exposure the subendothelial matrix proteins to the blood and result in thrombosis[124].

Oxidized low-density lipoprotein (ox-LDL), a strong pro-atherogenic factor, induces human umbilical vein endothelial cells (HUVECs) apoptosis and down-regulation of miR-126, which can be significantly reversed by miR-126 mimics[125]. Studies have found that downregulation of miR-126 inhibits the PI3K/Akt signaling, while overexpression of miR-126 significantly increased PI3K/Akt signaling as well as its downstream proteins, such as Bcl-2, Bad, and cleavage of caspase-9[126]. According to above results, miR-126 can stimulate Akt phosphorylation through targeting PIK3R2, and then inhibit vascular endothelial cells apoptosis in atherosclerosis-related models. Similarly, apoptosis of UVECs-CRL-1730 Cell Line induced by H_2O_2 is related to miR-126 down-regulation and reduction of PIK3R2 (p85β) inhibition[127]. MiR-126 is involved in HUVECs apoptosis via regulating the PI3K signal. It has been reported that P-PI3K, p-Akt, and p-mTOR are upregulated, while miR-126, caspase-3 activity, and apoptotic rate are downregulated simultaneously. MiR-126 mimics reverse the above state; however, the 740Y-P (a PI3K activator) inverts miR-126 mimic's effect by inhibiting PI3K/Akt/mTOR signal, suggesting that miR-126 exerts an anti-apoptotic effect by targeting PI3K/Akt signaling[125].

Despite the fact that most studies have recognized that miR-126 inhibits endothelial cell apoptosis, opinions on miR-126 regulating PI3K are mixed. There are even more conflicting opinions: endothelial cells apoptosis induced by ox-LDL is accompanied by overexpression of miR-126, miR-126 inhibitor transfecting endothelial cells inhibits ox-LDL-induced apoptosis, and the PI3K/Akt signaling pathway is continuously acti-

vated, suggesting that miR-126 inhibits the PI3K/Akt signaling pathway and promote endothelial cell apoptosis[128]. In conclusion, it remains unclear how miR-126 regulates endothelial cell apoptosis by targeting PI3K, and further research is needed.

MiR-126/VCAM-1 and PIK3R2 and Atherosclerosis-related Inflammation

Both basic research and clinical evidence show that chronic vascular inflammation is involved in the development of atherosclerosis[129]. Atherosclerosis is largely influenced by inflammation, from the formation of the atherosclerotic plaques to their eventual rupture[121,130]. Adhesion of monocytes to vascular endothelium is the key step in the early stages of atherogenesis, followed by the formation of foam cells and early plaque in the arterial intima. VCAM-1 is located on the surface of activated endothelial cells and is considered to be a key mediator of atherosclerosis, by specifically mediating the adhesion of monocytes and T lymphocytes to endothelial cells and promote the migration of leukocytes to the intima of blood vessels[131]. The combination of VCAM-1 with integrin triggers the signal cascade in endothelial cells, resulting in an increase of reactive oxygen species (ROS), inducing actin reorganization and destroying endothelial tight junction, which is the main mechanism of leukocyte migration from the vascular lumen to intima[132]. Studies have found that VCAM-1 is overexpressed only at the aortic plaque formation area[133], and targeted disruption of VCAM-1 inhibits the formation of early plaques in $Ldlr^{-/-}$ mice[134].

Overexpression of miR-126 significantly alleviated the progression of atherosclerosis and VCAM-1 expression, whereas inhibition of miR-126 is reversed[135]. Similarly, miR-126 expression was significantly downregulated, and VCAM-1 expression was significantly up-regulated in the $ApoE^{-/-}$ mouse model of atherosclerosis[136]. *In vivo*, atorvastatin treatment increased miR-126 levels, lowered VCAM-1 levels, and alleviated atherosclerotic lesions[136]. Cigarette smoke (CS) upregulated the expression of VCAM-1 and then stimulated vascular inflammation in $apoE^{-/-}$mice, while downregulating the miR-126[137]. These results showed that miR-126 can inhibit the adhesion of monocytes to endothelial cells by inhibiting VCAM-1 expression, and thereby alleviating arterial walls inflammation. Nevertheless, the opposite has also been found in some studies. For example, patients with coronary heart disease exhibited higher levels of both VCAM-1 and miR-126 (6.72 times) than healthy individuals[120]. It suggests that miR-126 and VCAM-1 expression are affected by multiple factors, which need to be refined. Overall, miR-126 targeting VCAM-1 is a new idea for treating atherosclerosis despite differing opinions.

Additionally, miR-126 inhibits inflammation by targeting PI3K in atherosclerosis. *In vitro* studies, paeonol promotes miR-126 expression in the rat thoracic aortic endothelial cells stimulated by ox-LDL, blocks the PI3K/Akt/NF-κB pathway, and inhibits the adhesion of monocytes to vascular endothelial cells[138]. In the absence of more support data, PI3K regulation of inflammation by mir-126 is evidently unstudied in atherosclerosis.

MiR-126/VEGF, EGFL7, PI3K, and Intra-Plaque Angiogenesis

Atherosclerotic plaques become increasingly vulnerable and rupture, resulting in luminal thrombosis, increasing the risk of cardiac and cerebrovascular events, such as stroke, dementia, and myocardial infarction. Intra-plaque angiogenesis, driven by local hypoxia[139], promotes atherosclerotic plaque development and plaque destabilization[140,141]. Physiologically, there is no neovascularization in the intima of arteries. With the accumulation of foam cells and proliferation of smooth muscle cells, plaques are gradually increasing, and hypoxia in the plaques is aggravating, thereby exacerbating angiogenesis in the plaques by stimulating medial nourishing vessels to enter the intima. VEGF and its receptor (VEGFR) have been identified as the major pathway involved in intra-plaques angiogenesis[142]. There was evidence that endothelial cells of intra-plaque neovascularization express higher concentrations of VEGF and VEGFR than those in the lumen of blood vessels[143]. Studies demonstrated that ox-LDL induced angiogenesis of HUVECs *in vitro*, in which VEGF-A induced endothelial cell proliferation and migration[144]. Furthermore, Li[145] found that overexpression of VEGF promotes endothelial cell migration, proliferation, and angiogenesis by activating the VEGF/VEGFR2 pathway. In addition, VEGF-A can induce MMP-2, MMP-9, and urokinase-type plasminogen by activating NF-κB. MMP-2/9 can degrade the basement membrane and extracellular matrix to allow migration of new endothelial cells, and then format capillary sprouts[146]. All these suggest that VEGF/VEGFR2 and its induced NF-κB signal participate in angiogenesis in atherosclerosis, stimulate plaque progression, and cause plaque unstable.

In general, the expression of miR-126 is high, and yet VEGF is low in endothelial cells, and there is a negative correlation between them. The overexpression of miR-126 down-regulates VEGF-A expression in cells, especially in non-endothelial cells, thus indirectly suppressing quiescent endothelial cell activation. As is well known, the enlargement of plaque volume will lead to local hypoxia of plaque and promote intra-plaque angiogenesis. Atherosclerotic patients showed an increase in VEGF-A with the increase of intima-media thickness (IMT) and plaque area, but a decrease in miR-126 expression, and indicating a significant negative correlation between miR-126 and VEGF-A[147]. To sum up, miR-126 down-regulation and VEGF-A up-regulation is the possible mechanism of intra-plaque angiogenesis. However, the direct evidence that miR-126 targeting VEGF inhibits intra-plaque angiogenesis is relatively insufficient at present and further research is needed.

EGFL7 is a secretory protein produced by vascular endothelial cells that participates in angiogenesis. There was an upregulation of EGFL7 in 11 of the 14 human atherosclerotic plaque samples compared with matched control samples (plaque adjacent areas), suggesting that elevated EGFL7 may lead to atherosclerosis[148]. In line with this, the EGFL7 was detected in both endothelial cells and vascular smooth muscle cells of atherosclerotic plaques, with the highest expression in proliferative endothelial cells[149]. Further research shows that transfecting recombinant plasmid plegfp-N1/miR-126 into endothelial cell line ECV-304 caused a reduction of 67% in EGFL7 protein expression compared to empty vector transfection group (only 6.5%) after 48h transfection, suggesting that miR-126 can reduce EGFL7 protein expression in ECV-304 cells[150]. In addition, miR-126 inhibits angiogenesis in HUVECs, as well as down-regulate EGFL7 mRNA and protein expression significantly[151]. In summary, miR-126 inhibits intra-plaque angiogenesis, at least in part, by targeting EGFL7.

Recently, PI3K has been found to be closely related to atherosclerosis-related angiogenesis. As a risk factor of atherosclerosis, low concentration ox-LDL can promote angiogenesis of human coronary artery endothelial cells (HCAECs) *in vitro* and activate the synthesis of nitric oxide via the PI3K/Akt/eNOS pathway[152]. It is known that eNOS can promote angiogenesis through Akt/PKA[153]. Therefore, PI3K and downstream pathway Akt/eNOS are important promoting factors of angiogenesis[153]. In addition, ox-LDL promotes the process of angiogenesis by relying on the nucleocytoplasmic shuttle of Id1, which was controlled by the PI3K pathway, and the inhibition of PI3K blocks the angiogenesis induced by ox-LDL[154]. It follows that PI3K participates in the angiogenesis of atherosclerosis through various mechanisms. Although it has been found that PI3K is regulated by miR-126 to participate in the angiogenesis of endothelial cells[155,156], the direct evidence of miR-126 regulates PI3K on the angiogenesis of atherosclerotic models is not established.

MiR-126/LRP6 and Vascular Smooth Muscle Proliferation

Low-density lipoprotein receptor-related protein 6 (LRP6), as a member of the low-density lipoprotein receptor family, is a co-receptor of the Wnt signaling pathway and plays an important role in atherosclerosis[157]. Excessive PDGF signaling detected in LRP-R611C mice is associated with activation of the Wnt signaling pathway and upregulation of Sp1 (a transcription factor known to target PDGF and PDGFR-β gene expression)[157]. Keramati et al[158] reported that human atherosclerotic coronary arteries overexpress and colocalize LRP6 and PDGFR-β. Wild-type LRP6 forms a complex with PDGFR-β, triggering its lysosomal degradation. This effect reduces the proliferation of vascular smooth muscle cells, which has a protective effect against atherosclerosis[158]. More studies have found that LRP6R611C mutation significantly activates PDGF signaling and increases smooth muscle proliferation, which promotes the occurrence and development of atherosclerosis[159]. The above studies suggest that LRP6 inhibits the proliferation of vascular smooth muscle induced by PDGFR-β, delaying atherosclerosis progression. Previous studies have found that miR-126 targets LRP6, suggesting that miR-126 is involved in atherosclerosis by targeting LRP6[28]. After miR-126 was transferred from endothelial microparticles into VSMCs, the proliferation of VSMCs and the formation of new intima, as well as LRP6 expression were inhibited[160], which is different from the previous conclusion. Consequently, miR-126 targeting LRP6 participates in the process of atherosclerosis by mediating the proliferation of smooth muscle cells, which needs further study.

MiR-126/CXCL12-CXCR4 Axis and Vascular insult, Neovascularization

CXCL12 plays important, complex, and even contradictory role in atherosclerosis, from proatherogenic, proinflammatory, and prothrombotic to

atheroprotective, plaque stabilizer, and dyslipidemia rectifier, mainly through its classical receptor CXCR4[161,162]. CXCR4 is widely expressed in various cell types that play a role in CVDs, such as endothelial progenitor cells (EPCs), endothelial cells, macrophages, platelets, and smooth muscle cells[162]. Similarly, high expression of CXCR4 and CXCL12 mRNA was also found in patients with carotid plaques[163]. Furthermore, they are also implicated in intraplaque neovascularization and thrombus formation in the advanced atherosclerotic plaques[164-167]. CXCL12 levels are also associated with hyperlipidemia and inflammation. For example, CXCL12 overexpression in ApoE$^{-/-}$ mice increases macrophage infiltration, inhibits reverse cholesterol transport, decreases plasma HDL-C levels, and then enlarges atherosclerotic lesions[168]. Through CXCL12/CXCR4 signaling, platelets involved in atherothrombosis[169] that is related to increased dense granule secretion and thromboxane A2 production[170]. In additional, CXCL12-CXCR4 axis controls the proliferation and migration of smooth muscle cells[171], promoting plaque formation, stabilization, and re-stenosis[172]. As mentioned above, the role of the CXCL12/CXCR4 axis in atherosclerosis is still controversial.

CXCL12 has been identified as a direct target of miR-126 by miRNA prediction in EPCs and miR-126 improves EPCs migration by targeting CXCL12[173,174]. Therefore, miR-126 may affect atherosclerosis by targeting CXCL12 and/or CXCR4. There are only a few studies suggesting that miR-126 negatively regulates CXCL12 to inhibit EPCs-mediated angiogenesis[173], but others have yielded contradictory results. For example, CXCL12 was found to promote angiogenesis in the aorta of SD rats with the overexpression of miR-126-3p, and its effect was eliminated by inhibiting of miR-126-3p[175]. This paradoxical phenomenon may be related to the fact that miR-126 also targets SPRED-1 and then affects the function of CXCL12[175]. So, research is needed to determine how miR-126 affects atherosclerosis by directly targeting the CXCL12-CXCR4 axis.

Association Between the Effects of MiR-126 on Atherosclerosis and Cancer

MiR-126 and Proliferation and Apoptosis Both of Cancer and Atherosclerosis

Cell proliferation and apoptosis are two opposite states of cells. In cancer lesions, cancer growth results from unchecked cell proliferation and inhibition of apoptosis; in atherosclerotic lesions, the apoptosis of endothelial cells coated on the lumen surface of arterial intima is the early initial event of atherosclerosis, while the proliferation of smooth muscle cells promotes the progression of atherosclerotic plaques. As mentioned above, miR-126 mainly targets inhibiting PI3K, VEGF, and EGFL7, participating in cell proliferation and apoptosis, and taking part in the process of cancer and atherosclerosis.

MiR-126 inhibits cancer cells proliferation and promote apoptosis by targeting PI3K/Akt signaling pathway, and participate in the progression of endometrial cancer[17], cervical cancer[39], non-small cell lung cancer[26], esophageal squamous cell carcinoma[18] and prostate cancer[25]. At the same time, in atherosclerosis-related models, miR-126 inhibits PIK3R2 (p85-β) regulating PI3K/Akt or PI3K/Akt/mTOR signaling pathway, further reduce the apoptosis rate of endothelial cells[125,126], and restrain the proliferation of VSMCs induced by ox-LDL, ultimately inhibiting atherosclerosis[176]. As mentioned above, PTEN acts as cancer-suppressor and an atherosclerosis-promoter. In non-small cell lung cancer A549 cells, miR-126 was found to inhibit PI3K/Akt signaling pathway by targeting PIK3R2, increasing the expression of PTEN and inhibiting the proliferation of cancer cells[26]. Interestingly, PTEN decreases VSMCs proliferation and migration, accelerating atherosclerosis, suggesting that PTEN is a potential target for miR-126 inhibiting smooth muscle proliferation[177].

As well as PI3K, VEGF and EGFL7 are also miR-126 regulatory signals, inhibit cancer proliferation, promote apoptosis, and participate in the process of cancer. Overexpression of miR-126-5p can inactivate VEGF-A/VEGFR2/ERK signaling pathway and promote apoptosis of non-small cell lung cancer H1299 cell line[50]. In ovarian cancer[88], renal cell carcinoma[95], liver cancer[87], oral squamous cell carcinoma [96], and non-small cell lung cancer [86], miR-126 can also inhibit cell proliferation and promote apoptosis by targeting EGFL7 signaling. Further studies have shown that the downstream signal of miR-126 targeting EGFL7 is ERK in hepatoma cell lines (HepG2, Bet-7402, and smmc-7721)[89]. In atherosclerosis-related cell models, ERK was found to mediate curcumin to inhibit HIF-1α-induced apoptosis of macrophages. It suggests that miR-126 can target VEGF or EGFL7 to affect ERK-mediated apoptosis of cancer cells and ath-

erosclerosis-related cells[178]. To sum up, despite the existence of different opinions, miR-126 regulates proliferation and apoptosis of cancer cells and atherosclerosis-related cells by targeting PI3K, VEGF, and EGFL7 at the same time.

MiR-126 Influences Angiogenesis in Both Cancers and Atherosclerosis

Angiogenesis is not only a necessary condition for cancer progression but also a factor in atherosclerotic plaque destabilization and rupture. Therefore, inhibition of angiogenesis is also an important point in the control of cancer and atherosclerosis. According to the above, miR-126 participates in angiogenesis in cancers and intra-plaques by targeting VEGF, PI3K, and EGFL7.

VEGF binding to VEGFRs on vascular endothelial cells promotes cancer angiogenesis. MiR-126 inhibits cancer angiogenesis in oral squamous cell carcinoma[32], liver cancer[52], gastric cancer[55], and breast cancer[57] by targeting VEGF expression. Down-regulation of miR-126 and up-regulation of VEGF are related to intra-plaque angiogenesis[147], suggesting that miR-126 may also reduce angiogenesis, and thereby stabilizing plaques by inhibiting VEGF expression. In gastric cancer cell lines, such as SGC-7901, MKN-28, and MKN-45, miR-126 could regulate the activity of Akt, mTOR, and ERK1/2 by targeting VEGF-A, and ultimately inhibit the growth and angiogenesis of gastric cancer[55]. Similarly, MMPs were induced by VEGF-A via activating NF-κB[146], which degrade the basement membrane and extracellular matrix to enable new endothelial cells to migrate, resulting in capillary sprouts in atherosclerosis[146]. MiR-126 negatively regulated VEGF/VEGFR2 and then NF-κB signaling to participate in angiogenesis of atherosclerosis and thereby causes plaque instability[179]. These suggests that miR-126 can inhibit cancer and atherosclerosis related angiogenesis by down-regulating VEGF.

In renal cancer[95] and liver cancer[87], miR-126 has been shown to affect cancer angiogenesis by regulating EGFL7; even more than that, miR-126 has also been found to inhibit EGFL7 in atherosclerosis, thereby inhibiting intra-plaques angiogenesis[150,151]. In the study of liver cancer, it was found that miR-126/EGFL7 partially inhibited angiogenesis by down-regulating the ERK signaling pathway[89], but there has been no further evidence of atherosclerosis.

MiR-126 Influences Inflammatory Responses in Cancers and Atherosclerosis

Inflammation is involved in the occurrence and development of both cancer and atherosclerosis, and miR-126 targets VCAM-1 to do so. The downregulation of VCAM-1 by MiR-126 reduces monocyte adhesion to endothelial cells caused by cigarette smoke, and alleviate the arterial wall inflammation[137]. Macrophages modulate VCAM-1 and integrin α4β1 and involve in the stimulation of breast cancer cell survival by electronic smoke[83]. It appears that the mechanisms of smoke-induced cancers and atherosclerosis have something in common, and miR-126 can prevent and treat them by inhibiting these mechanisms. MiR-126 can significantly inhibit the adhesion of monocytes to ox-LDL-activated rat thoracic aortic endothelial cells by down-regulating VCAM-1, thereby delaying the process of atherosclerosis[136]. Similarly, IL-1β-induced VCAM-1 may also modulate adhesion between glioblastomas cells and monocytes[84]. Accordingly, VCAM-1 is involved in monocyte adhesion and is inhibited by miR-126 in both cancer and atherosclerosis. In addition, cancer-associated macrophages contribute to the progression and Warburg effect of pancreatic ductal adenocarcinoma via the CCL18/NF-kB/VCAM-1 pathway[82]. According to these findings, miR-126 targeting VCAM-1 is involved in the inhibition of cancer and atherosclerotic disease development through multiple mechanisms.

MiR-126 participates in the pathological and pathophysiological processes of cancer and atherosclerosis by inhibiting PIK3R2, VEGF-A, VCAM-1, LRP6, and EGFL7. 1) In terms of cancer, miR-126 inhibits PIK3R2/PI3K/Akt pathway and regulates its downstream targets MRP1, mTOR, PTEN, ANLN, Snail, and caspase-3, and thereby affects drug resistance, proliferation, migration and invasion, apoptosis of cancer cells, delaying cancer progression. In terms of atherosclerosis, miR-126 inhibits PIK3R2/PI3K/Akt pathway and regulates downstream targets Caspase-3, mTOR and NF-κB, eNOS and Id1, and then affects endothelial cell apoptosis, inflammation and angiogenesis, slowing down the progress of atherosclerosis. 2) On one hand, miR-126 inhibits VEGF-A/VEGFR pathway and regulates its downstream target ERK, and then affects cancer migration, invasion, and apoptosis; on the other hand, MiR-126 inhibits VEGF-A/VEGFR pathway and regulates its downstream

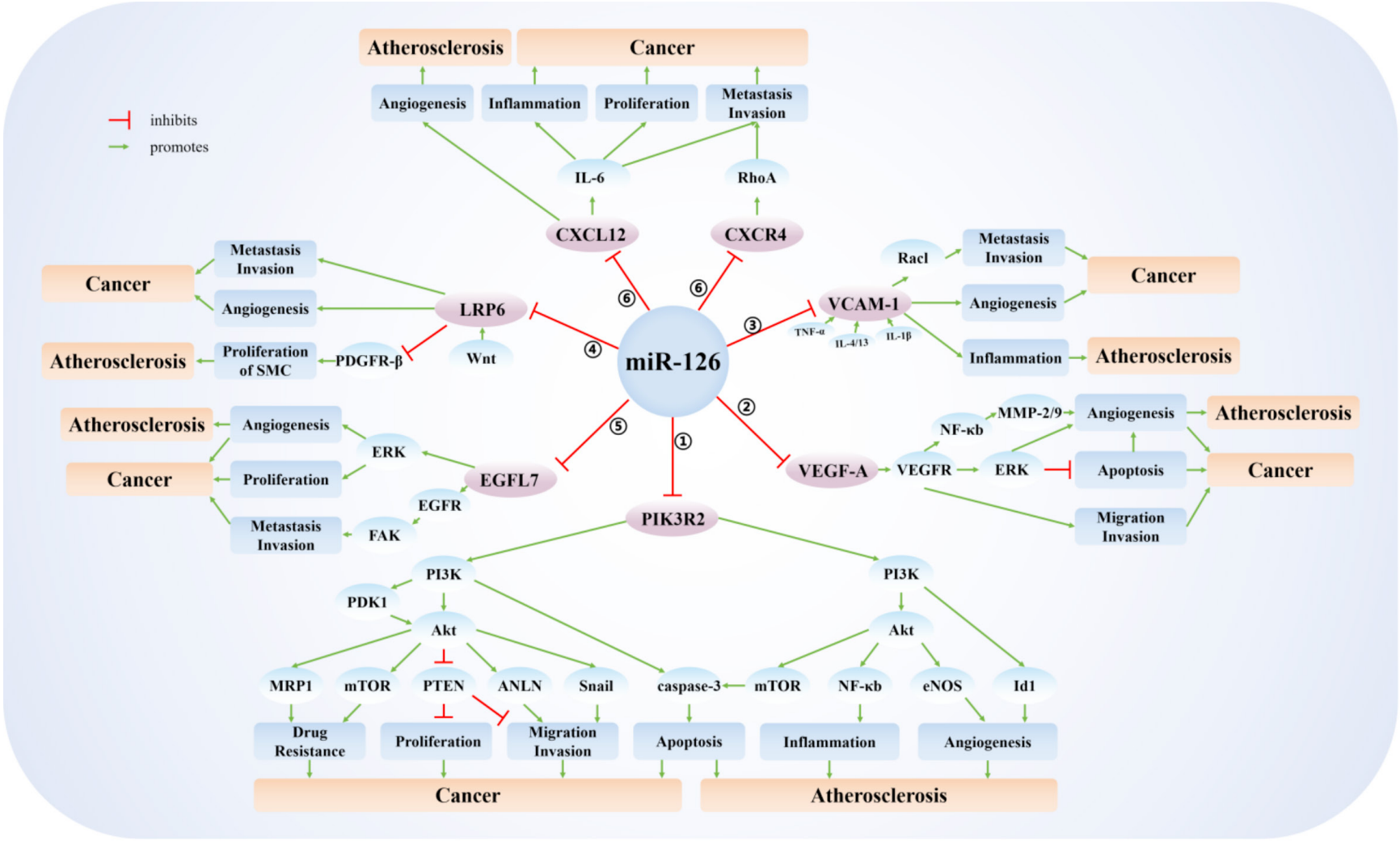

Figure 1. MiR-126 targets PI3K, VEGF, VCAM-1, EGFL7, CXCL12-CXCR4 axis, and LRP6 to involve in both cancer and atherosclerosis.

Table I. The role of miR-126 in cancer and atherosclerosis through common target genes.

Targets of miR-126		Effect on targets	Signaling pathways/effector molecule	Effect on pathways/ molecule	Disease	Expression of miR-126 in disease	Research object	Role of miR-126	Reference
PI3K	PIK3R2	-	Caspase-3	Promote	Endometrial carcinoma	Downregulated	RL95 and HEC1A cell	Inhibit proliferation and induce apoptosis	17
	PIK3R2	Inhibit	PTEN	Promote	Non-small cell lung cancer	Downregulated	A549 cell	Inhibit proliferation, metastasis and invasion	26
	-	-	PI3K/PDK1/Akt	-	Cervical cancer	Downregulated	HeLa cell	Promote apoptosis, inhibit proliferation and metastasis	39
	PIK3R2	Inhibit	PI3K/Akt	Inhibit	Esophageal squamous cell carcinoma	Downregulated	EC109 cell	Inhibit proliferation and metastasis	18
	PIK3R2	Inhibit	PI3K/Akt	Inhibit	Prostate cancer	Downregulated	DU145, PC-3 and 293T cell	Inhibit proliferation	25
	-	-	PI3K/Akt/Snail	Inhibit	Lung cancer	Downregulated	SPC-A1 and LLC cell	Inhibit metastasis	40
	PIK3R2	Inhibit	PI3K/Akt/MRP1	Inhibit	Gastric cancer	Downregulated	SGC-7901, BGC-823, SGC-7901/ DDP and BGC-823/DDP cell	Reduce drug resistance	46
	PIK3R2	Inhibit	PIK3R2/PI3K/Akt/mTOR	Inhibit	Breast cancer	Downregulated	SKBR3/TR cell	Reduce drug resistance	36
	PIK3R2	Inhibit	Akt	Promote	Atherosclerosis	Downregulated	CRL-1730 cell	Inhibit apoptosis	127
	-	-	PI3K/Akt	Promote		Downregulated	Human umbilical vein endothelial cells	Inhibit apoptosis	126
	-	-	PI3K/Akt/mTOR	Inhibit		Downregulated	Human umbilical vein endothelial cells	Inhibit apoptosis	125
	-	-	PI3K/Akt	Inhibit		Upregulated	Human umbilical vein endothelial cells	Promote apoptosis	128
	-	-	PI3K/Akt/NF-κB	Inhibit		Downregulated	Endothelial cells of rat thoracic aorta	Inhibit inflammation	138
VEGF	VEGFA	Inhibit	VEGF-A/VEGFR-2/ERK	Inhibit	Non-small cell lung cancer	Downregulated	NCI-H1299 cell	Promote apoptosis, inhibit metastasis and invasion	50
	VEGF	Inhibit	-	-	Ovarian cancer	Downregulated	SKOV3 cell	Inhibit proliferation, metastasis and invasion	56
	VEGF	Inhibit	-	-	Breast cancer	Downregulated	Breast cancer mice	Inhibit metastasis	58
	VEGF-A	Inhibit	-	-	Ovarian cancer	Downregulated	SKOV3 and ES2 cell	Inhibit invasion and metastasis	53
	VEGF-A	Inhibit	Akt, mTOR and ERK1/2	-	Gastric cancer	Downregulated	SGC-7901, MKN-28 and MKN-45 cell	Inhibit angiogenesis	55
	VEGF-A	Inhibit	-	-	Liver cancer	Downregulated	HepG2 cell	Inhibit angiogenesis	52
	VEGF-A	Inhibit	-	-	Breast cancer	Downregulated	MCF cell	Promote apoptosis, inhibit proliferation and angiogenesis	57
	VEGF-A	Inhibit	-	-	Atherosclerosis	Downregulated	Atherosclerotic patients	Reduce intima-media thickness and plaque area	147
VCAM-1	VCAM-1	Inhibit	-	-	Prostate cancer	Downregulated	PC3 and DU145 cell	Inhibit metastasis	66
	VCAM-1	Inhibit	-	-	Chronic myelogenous leukemia	Downregulated	LAMA84 cell	Inhibit metastasis and invasion	68
	VCAM-1	Inhibit	-	-	Chondrosarcoma	Downregulated	JJ012 cell	Inhibit metastasis and invasion	67
	VCAM-1	Inhibit	-	-	Atherosclerosis	Downregulated	$ApoE^{-/-}$ mice; rat thoracic aorta endothelial cell	Inhibit inflammation	136
	VCAM-1	Inhibit	-	-		Downregulated	$ApoE^{-/-}$ mice	Inhibit inflammation	137
EGFL7	EGFL7	Inhibit	ERK	Inhibit	Liver cancer	Downregulated	Nude mouse liver cancer model; hepG2, Bet-7402 and smmc-7721 cell	Promote apoptosis, inhibit proliferation and angiogenesi	8
	EGFL7	Inhibit	-	-	Non-small cell lung cancer	Downregulated	A549 cell	Inhibit proliferation and promote apoptosis	86
	EGFL7	Inhibit	-	-	Ovarian cancer	Downregulated	Ovarian cancer patients	Inhibit metastasis and invasion	88
	EGFL7	Inhibit	-	-	Renal cell carcinoma	Downregulated	Renal carcinoma mouse model	Inhibit metastasis and angiogenesis	95
	EGFL7	Inhibit	-	-	Liver cancer	Downregulated	Nude mouse liver cancer model	Inhibit angiogenesis	87
	EGFL7	Inhibit	-	-	Atherosclerosis	Downregulated	ECV-304 cell	Inhibit angiogenesis	150
	EGFL7	Inhibit	-	-		Downregulated	Human umbilical vein endothelial cells	Inhibit angiogenesis	151
LRP6	LRP6	Inhibit	-	-	Liver cancer	Downregulated	Clinical liver cancer tissue and normal liver tissue; L02 cell, HepG2 cell, SMMC-7721 cell, BEL-7402 cell	Inhibit migration, invasion and angiogenesis	28
	LRP6	Inhibit	-	-	Atherosclerosis	-	Smooth muscle cells	Inhibit proliferation	160

target NF-κB and MMP-2/9, and then affects angiogenesis, participating in the progress of atherosclerosis. 3) MiR-126 inhibits VCAM-1 and regulates downstream target Racl, and then affects angiogenesis, cancer cell migration and invasion, participating in cancer progression. MiR-126 inhibits VCAM-1 to affect endothelial inflammation, participating in the progression of atherosclerosis. 4) MiR-126 inhibits LRP6 and then affects cancer cell migration and invasion, angiogenesis, participating in cancer progression. MiR-126 inhibits LRP6-β and regulates PDGFR, and then affects the proliferation of vascular smooth muscle cells, involving in the progression of atherosclerosis. 5) MiR-126 inhibits EGFL7 and regulates downstream targets EGFR, FAK, and ERK, and then affects cancer cell migration and invasion, proliferation and angiogenesis, participating in cancer progression. MiR-126 inhibits EGFL7/ERK, and then affects angiogenesis, participating in the progression of atherosclerosis. 6) MiR-126 inhibits CXCL12/CXCR4 and regulates downstream targets IL-6 and RhoA, and then affects cancer cell inflammation, proliferation, migration and invasion, participating in cancer progression. MiR-126 inhibits CXCL12, and then affects angiogenesis, participating in the progression of atherosclerosis. α4β1, α4β1 integrin.

Clinical Application of MiR-126 in Cancer and Atherosclerosis

MiR-126 has aroused great interest as a new biomarker for the diagnosis and treatment of cancers and atherosclerosis and related cardio-cerebrovascular diseases. Several studies have confirmed the diagnostic and prognostic value of miR-126 in lung cancer[180-184]. In addition, miR-126 is also identified as a specific diagnostic marker and new therapeutic target for ovarian cancer[185], colorectal cancer[186], gastric cancer[187], hepatocellular carcinoma[188], esophageal squamous cell carcinoma[189], prostate cancer[190], glioma [191] and breast cancer[27,192,193]. Similarly, recent studies have started to unveil the potentially important function of miR-126 in atherosclerosis and related cardio-cerebrovascular diseases[25,194]. In addition, miR-126 may be considered as a diagnosis biomarker by using blood-based non-invasive methods, in atherosclerosis[195], acute myocardial infarction[196], ischemic stroke[197]and diabetic vasculopathy[198].

Conclusions

MiR-126 is a small RNA highly expressed in endothelial cells, which is closely related to cancer and atherosclerosis. Thus, miR-126 is regarded as a potentially important target for the intervention of cancer and atherosclerosis. But how miR-126 can kill two birds with one stone: benefit both malignant cancers and atherosclerosis remains a mystery. At present, the main point of view is that the over-expression of miR-126 is beneficial to atherosclerosis and cancerogenesis, which is due to different mechanisms of miR-126 function. The underlying mechanisms of miR-126 are involved in multiple effects and multiple targets (Figure 1 and Table I): 1) miR-126 targets PIK3R2, VEGF, and EGFL7 genes to promote cancer cell apoptosis and inhibit apoptosis of endothelial cell and proliferation of VSMCs related to atherosclerosis. 2) miR-126 targets PIK3R2, VEGF, VCAM-1, and EGFL7, inhibits cancer angiogenesis, delays cancer progression, inhibits intra-plaques angiogenesis, stabilizes vulnerable plaques, and reduces the occurrence of complications such as thrombosis. 3) miR-126 inhibits the inflammatory response of cancers and atherosclerosis by targeting VCAM-1 and PIK3R2. In conclusion, miR-126 affects cancer and atherosclerosis via inhibiting cell proliferation, promoting apoptosis, inhibiting angiogenesis, and inhibiting inflammatory response, which provides a new idea for clinical treatment of cancer and atherosclerosis. However, there are still contradictory results related to the characteristics of environmental dependence and target diversity of miR-126. Further intensive studies are needed to explore the molecular and biological functions of miR-126 in cancer and atherosclerosis.

Conflict of Interest

The authors declare that the paper was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

Qiuyue Yang and Qun Yu drafted the manuscript. Xijuan Jiang and Jiali Gan designed and supervise manuscript. Wenyun Zeng verified the contents and revised the manuscript. Miao Zeng, Xiaolu Zhang, Yilin Zhang, Lin Guo critically revised the manuscript. All authors reviewed and approved the final manuscript.

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