SPANDIDOS PUBLICATIONS

BIOMEDICAL REPORTS 4: 131-134, 2016

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

WEINA HUANG[1], JIE LIN[2] and HONGXUAN ZHANG[3]

[1]The First Clinical Medical College; [2]Department of Pathology, Southern Medical University, Guangzhou, Guangdong 510515; [3]Department of Critical Care and Emergency, Guangdong General Hospital, Guangdong Academy of Medical Science, Guangdong Geriatric Institute, Guangzhou, Guandong 510080, P.R. China

Received October 13, 2015; Accepted November 25, 2015

DOI: 10.3892/br.2015.549

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.

Contents

Correspondence to: Dr Hongxuan Zhang, Department of Critical Care and Emergency, Guangdong General Hospital, Guangdong Academy of Medical Science, Guangdong Geriatric Institute, 106 Zhongshan Road 2, Guangzhou, Guandong 510080, P.R. China
E-mail: 13602816365@139.com

Key words: microRNA-126, colon cancer, tumor metastasis, biomarker

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 p85β 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-κB (NF-κB) 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-κB 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.

Acknowledgements

The present study was supported by the Pearl River Science and Technology New Star Foundation of Guangzhou City (grant no. 2012J2200044).

References

1. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J and Bouvier AM: Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 244: 254-259, 2006.
2. Siegel R, Naishadham D and Jemal A: Cancer statistics, 2012. CA Cancer J Clin 62: 10-29, 2012.
3. Bartel DP: MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell 116: 281-297, 2004.
4. Bartel DP: MicroRNAs: Target recognition and regulatory functions. Cell 136: 215-233, 2009.
5. He L and Hannon GJ: MicroRNAs: Small RNAs with a big role in gene regulation. Nat Rev Genet 5: 522-531, 2004.
6. Wang S, Aurora AB, Johnson BA, Qi X, McAnally J, Hill JA, Richardson JA, Bassel-Duby R and Olson EN: The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. Dev Cell 15: 261-271, 2008.
7. Saito Y, Friedman JM, Chihara Y, Egger G, Chuang JC and Liang G: Epigenetic therapy upregulates the tumor suppressor microRNA-126 and its host gene EGFL7 in human cancer cells. Biochem Biophys Res Commun 379: 726-731, 2009.
8. Meister J and Schmidt MH: miR-126 and miR-126*: New players in cancer. ScientificWorldJournal 10: 2090-2100, 2010.
9. Li N, Li X, Huang S, Shen S and Wang X: miR-126 inhibits colon cancer proliferation and invasion through targeting IRS1, SLC7A5 and TOM1 gene. Zhong Nan Da Xue Xue Bao Yi Xue Ban 38: 809-817, 2013 (In Chinese).
10. Li Z, Li N, Wu M, Li X, Luo Z and Wang X: Expression of miR-126 suppresses migration and invasion of colon cancer cells by targeting CXCR4. Mol Cell Biochem 381: 233-242, 2013.
11. Jia AY, Castillo-Martin M, Bonal DM, Sánchez-Carbayo M, Silva JM and Cordon-Cardo C: MicroRNA-126 inhibits invasion in bladder cancer via regulation of ADAM9. Br J Cancer 110: 2945-2954, 2014.
12. Guo C, Sah JF, Beard L, Willson JK, Markowitz SD and Guda K: The noncoding RNA, miR-126, suppresses the growth of neoplastic cells by targeting phosphatidylinositol 3-kinase signaling and is frequently lost in colon cancers. Genes Chromosomes Cancer 47: 939-946, 2008.
13. Feng R, Chen X, Yu Y, Su L, Yu B, Li J, Cai Q, Yan M, Liu B and Zhu Z: miR-126 functions as a tumour suppressor in human gastric cancer. Cancer Lett 298: 50-63, 2010.
14. Png KJ, Halberg N, Yoshida M and Tavazoie SF: A microRNA regulon that mediates endothelial recruitment and metastasis by cancer cells. Nature 481: 190-194, 2012.
15. Long G, Wang F, Duan Q, Chen F, Yang S, Gong W, Wang Y, Chen C and Wang DW: Human circulating microRNA-1 and microRNA-126 as potential novel indicators for acute myocardial infarction. Int J Biol Sci 8: 811-818, 2012.
16. Yin J, Bai Z, Song J, Yang Y, Wang J, Han W, Zhang J, Meng H, Ma X, Yang Y, *et al*: Differential expression of serum miR-126, miR-141 and miR-21 as novel biomarkers for early detection of liver metastasis in colorectal cancer. Chin J Cancer Res 26: 95-103, 2014.
17. Zhang T, Lv C, Li L, Chen S, Liu S, Wang C and Su B: Plasma miR-126 is a potential biomarker for early prediction of type 2 diabetes mellitus in susceptible individuals. Biomed Res Int 2013: 761617, 2013.
18. Chen J and Huang XF: The signal pathways in azoxymethane-induced colon cancer and preventive implications. Cancer Biol Ther 8: 1313-1317, 2009.
19. Vargas PA and Alberts DS: Primary prevention of colorectal cancer through dietary modification. Cancer 70 (Suppl 5): 1229-1235, 1992.
20. Leonardi T, Vanamala J, Taddeo SS, Davidson LA, Murphy ME, Patil BS, Wang N, Carroll RJ, Chapkin RS, Lupton JR, *et al*: Apigenin and naringenin suppress colon carcinogenesis through the aberrant crypt stage in azoxymethane-treated rats. Exp Biol Med (Maywood) 235: 710-717, 2010.
21. Warren CA, Paulhill KJ, Davidson LA, Lupton JR, Taddeo SS, Hong MY, Carroll RJ, Chapkin RS and Turner ND: Quercetin may suppress rat aberrant crypt foci formation by suppressing inflammatory mediators that influence proliferation and apoptosis. J Nutr 139: 101-105, 2009.
22. Vanamala J, Leonardi T, Patil BS, Taddeo SS, Murphy ME, Pike LM, Chapkin RS, Lupton JR and Turner ND: Suppression of colon carcinogenesis by bioactive compounds in grapefruit. Carcinogenesis 27: 1257-1265, 2006.
23. Chiou YS, Tsai ML, Nagabhushanam K, Wang YJ, Wu CH, Ho CT and Pan MH: Pterostilbene is more potent than resveratrol in preventing azoxymethane (AOM)-induced colon tumorigenesis via activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway. J Agric Food Chem 59: 2725-2733, 2011.
24. Xiao H, Hao X, Simi B, Ju J, Jiang H, Reddy BS and Yang CS: Green tea polyphenols inhibit colorectal aberrant crypt foci (ACF) formation and prevent oncogenic changes in dysplastic ACF in azoxymethane-treated F344 rats. Carcinogenesis 29: 113-119, 2008.
25. Afaq F, Saleem M, Krueger CG, Reed JD and Mukhtar H: Anthocyanin- and hydrolyzable tannin-rich pomegranate fruit extract modulates MAPK and NF-kappaB pathways and inhibits skin tumorigenesis in CD-1 mice. Int J Cancer 113: 423-433, 2005.
26. Malik A, Afaq F, Sarfaraz S, Adhami VM, Syed DN and Mukhtar H: Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. Proc Natl Acad Sci USA 102: 14813-14818, 2005.
27. Adams LS, Seeram NP, Aggarwal BB, Takada Y, Sand D and Heber D: Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppress inflammatory cell signaling in colon cancer cells. J Agric Food Chem 54: 980-985, 2006.
28. Kasimsetty SG, Bialonska D, Reddy MK, Ma G, Khan SI and Ferreira D: Colon cancer chemopreventive activities of pomegranate ellagitannins and urolithins. J Agric Food Chem 58: 2180-2187, 2010.
29. Banerjee N, Kim H, Talcott S and Mertens-Talcott S: Pomegranate polyphenolics suppressed azoxymethane-induced colorectal aberrant crypt foci and inflammation: Possible role of miR-126/VCAM-1 and miR-126/PI3K/AKT/mTOR. Carcinogenesis 34: 2814-2822, 2013.
30. Luo J, Manning BD and Cantley LC: Targeting the PI3K-Akt pathway in human cancer: rationale and promise. Cancer Cell 4: 257-262, 2003.
31. Leystra AA, Deming DA, Zahm CD, Farhoud M, Olson TJ, Hadac JN, Nettekoven LA, Albrecht DM, Clipson L, Sullivan R, *et al*: Mice expressing activated PI3K rapidly develop advanced colon cancer. Cancer Res 72: 2931-2936, 2012.

32. Harris TA, Yamakuchi M, Ferlito M, Mendell JT and Lowenstein CJ: MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1. Proc Natl Acad Sci USA 105: 1516-1521, 2008.
33. Maurer CA, Friess H, Kretschmann B, Wildi S, Müller C, Graber H, Schilling M and Büchler MW: Over-expression of ICAM-1, VCAM-1 and ELAM-1 might influence tumor progression in colorectal cancer. Int J Cancer 79: 76-81, 1998.
34. Li XM, Wang AM, Zhang J and Yi H: Down-regulation of miR-126 expression in colorectal cancer and its clinical significance. Med Oncol 28: 1054-1057, 2011.
35. Wang XY, Wu MH, Liu F, Li Y, Li N, Li GY and Shen SR: Differential miRNA expression and their target genes between NGX6-positive and negative colon cancer cells. Mol Cell Biochem 345: 283-290, 2010.
36. Li N, Tang A, Huang S, Li Z, Li X, Shen S, Ma J and Wang X: miR-126 suppresses colon cancer cell proliferation and invasion via inhibiting RhoA/ROCK signaling pathway. Mol Cell Biochem 380: 107-119, 2013.
37. Majka M, Janowska-Wieczorek A, Ratajczak J, Kowalska MA, Vilaire G, Pan ZK, Honczarenko M, Marquez LA, Poncz M and Ratajczak MZ: Stromal-derived factor 1 and thrombopoietin regulate distinct aspects of human megakaryopoiesis. Blood 96: 4142-4151, 2000.
38. Wang SC, Lin JK, Wang HS, Yang SH, Li AF and Chang SC: Nuclear expression of CXCR4 is associated with advanced colorectal cancer. Int J Colorectal Dis 25: 1185-1191, 2010.
39. Kijowski J, Baj-Krzyworzeka M, Majka M, Reca R, Marquez LA, Christofidou-Solomidou M, Janowska-Wieczorek A and Ratajczak MZ: The SDF-1-CXCR4 axis stimulates VEGF secretion and activates integrins but does not affect proliferation and survival in lymphohematopoietic cells. Stem Cells 19: 453-466, 2001.
40. Yasuoka H, Tsujimoto M, Yoshidome K, Nakahara M, Kodama R, Sanke T and Nakamura Y: Cytoplasmic CXCR4 expression in breast cancer: Induction by nitric oxide and correlation with lymph node metastasis and poor prognosis. BMC Cancer 8: 340, 2008.
41. Kollmar O, Rupertus K, Scheuer C, Junker B, Tilton B, Schilling MK and Menger MD: Stromal cell-derived factor-1 promotes cell migration and tumor growth of colorectal metastasis. Neoplasia 9: 862-870, 2007.
42. Heckmann D, Laufs S, Maier P, Zucknick M, Giordano FA, Veldwijk MR, Eckstein V, Wenz F, Zeller WJ, Fruehauf S, *et al*: A Lentiviral CXCR4 overexpression and knockdown model in colorectal cancer cell lines reveals plerixafor-dependent suppression of SDF-1α-induced migration and invasion. Onkologie 34: 502-508, 2011.
43. Chang YW, Marlin JW, Chance TW and Jakobi R: RhoA mediates cyclooxygenase-2 signaling to disrupt the formation of adherens junctions and increase cell motility. Cancer Res 66: 11700-11708, 2006.
44. Struckhoff AP, Rana MK and Worthylake RA: RhoA can lead the way in tumor cell invasion and metastasis. Front Biosci (Landmark Ed) 16: 1915-1926, 2011.
45. Cavallaro U and Christofori G: Cell adhesion and signalling by cadherins and Ig-CAMs in cancer. Nat Rev Cancer 4: 118-132, 2004.
46. Jiang W, Wang Q, Chen S, Gao S, Song L, Liu P and Huang W: Influenza A virus NS1 induces G0/G1 cell cycle arrest by inhibiting the expression and activity of RhoA protein. J Virol 87: 3039-3052, 2013.
47. Cortez MA and Calin GA: MicroRNA identification in plasma and serum: A new tool to diagnose and monitor diseases. Expert Opin Biol Ther 9: 703-711, 2009.