

The relationship between miRNA and colon cancer

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Abstract: Cancer of Colon (CRC) is one of the most common gastrointestinal malignancies in the world and the third most common cancer in the world^[1]. Clinically, markers such as carcinoembryonic antigen (CEA) are widely used in early treatment, but their sensitivity is poor, especially in diagnosis and treatment. In order to improve the efficiency of diagnosis and treatment of early CRC, it is necessary to find new sensitive biomarkers. In recent years, more and more attention has been paid to the role of exosomes in human malignant tumors. Studies have shown that plasma exosome microRNAs (miRs) mediate the occurrence, development, invasion, metastasis and other biological behaviors of tumors^[2-3]. At present, radical surgical treatment is often used in clinical treatment. There are certain limitations in combining chemotherapy and other means after surgery, and the toxic and side effects of patients are more prominent, bringing severe pain to patients. TCM treatment has certain advantages, so finding drugs that can efficiently kill tumor cells and have little toxic and side effects is a hot spot in the research and development of anti-tumor new drugs today^[4].

Keywords: miRNA, colon cancer, exosome

1. Relationship between plasma exosome and colon cancer

1.1. Outside the body

Exosomes are 40-100 nm in diameter, and their surface is rich in lipids such as cholesterol, sphingomyelin and ceramide. They contain biological information such as protein, mRNA and Micro RNA, and play an important role in the cell microenvironment. Johnstone et al. first discovered in 1983 that mature sheep reticulocytes could release a membranous vesicle, which was initially thought to be used to expel excess transferrin receptors and named as exosomes. Exosomes are not only the product of normal physiological and pathological metabolism of cells, but also secretion of exosomes is a universal cellular function^[5]. However, each content is different. After the vesicle transport mechanism was discovered, exosomes became one of the important carriers of intercellular signaling molecules. It mediates cell-to-cell communication through transporters, nucleic acids and other bioactive components.

1.2. Colon cancer and tissue microenvironment

Colon cancer is a common malignant tumor. The metastasis of colon cancer mainly includes transblood metastasis, peritoneal metastasis and lymph node metastasis, etc. The most common organ of metastasis is liver. Because mesenteric vessels drain to portal vein in anatomical structure, the probability of liver metastasis of colon cancer is higher.

Tissue microenvironment plays an important role in the initiation and metastasis of tumor. The tissue microenvironment of the target organ of metastasis will be transformed into pre-metastasis microenvironment, and then transformed into an environment suitable for the growth of tumor cells. The pre-metastasis environment of tumors specifically refers to the microenvironment in which the primary tumor is prepared for distant spread and colonization of tumor cells. The six characteristics of this microenvironment include inflammation, immunosuppression, angiogenesis/vascular permeability, organophilia, reprogramming and lymphangiogenesis^[6]. In mouse models of hepatic metastasis of pancreatic cancer and lung metastasis of melanoma, it has been proved that exosomes derived from tumor cells accelerate tumor metastasis by promoting the formation of premetastasis microenvironment, and exosomes are found to be an important factor regulating the formation of premetastasis microenvironment.

2. Relationship between miRNA of different exosomes and colon cancer

Studies have shown ^[7] that the expression profile of exosome miRNA is different in different stages of tumor development. Among them, the expressions of Mir-1246, Mir-150, Mir-21 and Mir-92a were increased during tumor development. Analysis of the expression of miRNA systems in multiple tumor samples revealed that the exosomes secreted by colon tumor cells are different from those secreted by normal cells because miRNA can carry important genetic information.

2.1. Expression of Mir-1246 in colon cancer

Mir-124 is a typical stem-loop structure. Many studies have shown that Mir-1246 is controlled by the P53 pathway. It has been reported that members of the P53 family have anticancer activities, mainly regulating the expression of target genes at the transcriptional level ^[8]. Mature Mir-1246 and its complementary mRNA usually negatively regulate target genes through two mechanisms dependent on sequence complementarity.

Baraniskin et al. ^[9] believed that miR1246 was a serum tumor marker for pancreatic ductal adenocarcinoma and colon cancer. Serum analysis of primary human ductal adenocarcinoma of the pancreas (PDAC) nude mice showed that miR1246 could be hybridized with RNU2-1 fragment (RNU2-1F) in patient serum. It is suggested that Mir-1246 can be released by target cells into the blood, emulsion and catheter fluid, but the release of miRNA is selective, and the selected release of miRNA may be associated with malignant tumors. This indicates that Mir-1246 is also correlated with colon cancer.

2.2. Relationship between Mir-150 and colon cancer

MiRNA is a class of small non-coding RNAs that negatively regulate the expression of target genes by interacting with the mRNA 3' non-coding region of target genes, thus participating in a variety of cytological functions, including cell proliferation, apoptosis, differentiation, metabolism and regulation of endocrine system. Abnormal miRNA expression is associated with a variety of diseases including tumors. It has been found in tumor studies that miRNA is involved in the regulation of tumor cell proliferation, apoptosis, differentiation, drug resistance, invasion and metastasis, among which Mir-150 also plays an important role in the occurrence and development of tumors. Down-regulated mir-150 expression promotes tumor progression in colon cancer ^[10].

Chen et al. ^[11] found that the expression level of Mir-150 in colon cancer tissues was low. Moreover, there are many studies in the field of immune system and hematopoietic system. Studies have found that Mir-150 is also abnormally expressed in most solid tumor tissues. Wu et al. ^[12] confirmed that Mir-150 has oncogenic activity at the cellular level and promotes the proliferation of gastric cancer cells by inhibiting the expression of proto-oncogene EGR2, thus participating in the occurrence and development of tumors. More and more scholars have confirmed the low expression of Mir-150 in colon cancer tissues, which is different from many solid tumors.

2.3. Expression of Mir-21 in tumor cells

Mir-21, located on chromosome 17Q23.1, plays a similar role to proto-oncogene and promotes malignant tumor progression by participating in the regulation of cell cycle and gene expression. It has been reported that Mir-21 can inhibit apoptosis and regulatory pathways, thus promoting the occurrence and progression of cancer ^[13]. A large number of data indicate that Mir-21 is a non-coding RNA closely related to tumor genesis and development, and it participates in regulating multiple aspects of tumor progression through targets of different genes. On the one hand, mir-21 is a good indicator for early diagnosis and prognosis due to the significant differential expression between tumor and healthy individuals. On the other hand, exosome Mir-21 is involved in the progression and drug resistance of a variety of tumors by regulating the expression of receptor cell target genes ^[14]. Numerous studies have found that the tumor microenvironment of mesenchymal cells and tumor cells themselves can release of high concentration miR - 21 secrete body outside, outside these secrete body can be caused by tumor cells to absorb around tumor cell phenotypic changes, at the same time, secrete body can be released into the blood or other body fluids involved in tumor metastasis and other biological processes ^[15].

2.4. Relationship between Mir-92a and colon cancer

Cluster Mir-17-92 is the first discovered oncogene, which can be divided into four different families

according to the homology of its gene sequence: Mir-17 family, Mir-18 family, Mir-19 family and Mir-92 family. Abnormal expression of Mir-92a family has been detected in a variety of tumors, and the abnormal expression of Mir-92a family is related to the occurrence and development of tumors. It can be found that Mir-92a family may have potential value as tumor markers [16]. Ng et al. found that mir-92a expression level was unrelated to TNM stage and tumor location. The plasma Mir-92a levels of patients with gastric cancer and inflammatory bowel disease were compared with those of healthy controls.

3. Research progress and prospect of exosomes as carriers of Traditional Chinese medicine

With the deepening of exosome research, more and more evidences show that exosome participate in the genesis and development of tumor through the delivery of Mir-. The expression of exosome Mir-in tumors, its value in early diagnosis and prognosis, and the molecular mechanism and related signal transduction pathways that regulate malignant biological behavior of tumors will become the focus of future research.

The involvement of exosomes in the development of colon cancer mostly starts from influencing its internal environment, and then participates in the occurrence, metastasis, immunity and drug resistance of colon cancer. Chinese medicine also intervenes in tumor treatment from the above aspects, so there is some relationship between Chinese medicine and exosome. Exosome has shown a good prospect in the diagnosis and treatment of colon cancer, but more studies are needed to prove the deep understanding of exosome, especially the relationship between Chinese medicine and exosome in the treatment of tumors. It remains to be solved to study the effect of Chinese medicine on tumor exosomes and explore a new development path of Chinese medicine for colon cancer treatment from the microscopic point of view.

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References

- [1] Zhu Yingchao, Hu Fei, Bu Shizhong. *Research progress of obesity and colon cancer [J]. Chem Biol*, 2020, 40(04): 585-592.
- [2] Xue Yuan, Li Peidong, Zhang Guangjun. *Research progress of microRNAs of serum exosomes in patients with colorectal cancer [J]. Chin J general gynecol clin*, 2020, 27(09): 1169-1174.
- [3] Ingenito F, Roscigno G, Affinito A, et al. *The role of exo-miRNAs in cancer: a focus on therapeutic and diagnostic applications. Int J Mol Sci*, 2019, 20(19): E4687.
- [4] Zhang Tao, Kang Xiangdong. *Research progress of traditional Chinese and western medicine in the treatment of colon cancer [J]. Systemic medicine*, 2019, 4(23): 192-194.
- [5] Li Xiao, Liu Lingying, Chai Jiake. *Journal of PLA medical college*, 2015, 36(10): 1042-1044+1051. (In Chinese)
- [6] Fu Yawen, Gao Feng, DuYuzhen. *The role of exosomes in the formation of microenvironment before tumor metastasis [J]. Modern oncology*, 2020, 28(23): 4167-4170.
- [7] Liu Hang, Li Xian, Zhang Lin, Wang Guanghui, Ding Jie. *Progress and significance of exosomal miRNA in diagnosis of colorectal cancer [J]. Medical review*, 2020, 26(21): 4219-4224.
- [8] Suzuki H, Yamagata K, Sugimoto K, et al. *Modulation of microRNA processing by Modulation of p53 [J]. Nature*, 2009, 460 (7254): 529-533.
- [9] Baraniskin A, Maike A, Steffen GJ, et al. *Circulating U2 small nuclear RNA fragments as a novel diagnostic biomarker for pancreatic and colorectal Adenocarcinoma [J]. Int J Cancer*, 2013, 132 (2): e48-E57.
- [10] Sun W. *The role of Mir-150 in the proliferation and metastasis of hepatocellular carcinoma and its related mechanisms [D]. Fourth Military Medical University*, 2016.
- [11] Chen X, Xu X, Pan B, et al. *miR-150-5p suppresses tumor progression by targeting VEGFA in colorectal cancer [J]. Aging (Albany NY)*, 2018, 10(11): 3421-3437.
- [12] Wu Q, Jin H, Yang Z, et al. *Negatively-regulating function of mir-150 and negatively regulating the pro-apoptotic gene EGR2 [J]. Biochem Biophys Res Commun*, 2010, 392 (3): 340-345.
- [13] Liu Jie, Zhang Wentian, DU Jinbo. *Expression of Mir-21 and C-Met in colon cancer and its clinical significance [J]. China medical review*, 2020, 17(17): 121-124.
- [14] Ma Q, Ma Q, Ma J, et al. *The effect of astrocyte exosome Mir-21 on the migration of pancreatic*

cancer cells and SERP1, a prognostic marker of pancreatic cancer [J]. Peking Union Medical College, 2018.

[15] Au Yeung CL, Co NN, Tsuruga T, et al: Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF 1. Nat Commun 7: 11150, 2016

[16] Guo Shuchuang. Expression of serum exosome Mir-92a in colorectal cancer and its prognostic significance [D]. Southern Medical University, 2020.