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# Research progress of miR-373 in gastrointestinal malignancies

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## Abstract

microRNAs are a kind of higher eukaryotic genomic coding, usually non-coding small single-stranded RNA composed of 19-24 nucleotides, similar to siRNA molecules, which can be paired with the mRNA base of targeted genes, guide the MRNA to directly degrade or inhibit transcription translation, regulate the expression of targeted genes, and affect the expression of targeted proteins. It has a profound effect on the function of cells in the human body. The abnormal expression of miRNA can affect the biological behavior of human cells and promote the occurrence and development of various types of diseases, such as malignant tumor diseases. miR-373 can participate in cell apoptosis, differentiation, proliferation, migration and invasion, as well as inflammatory response and viral infection. As a specific biological indicator for clinical evaluation of neoplastic diseases, Mir-373 is of great significance for the occurrence and development of diseases. Because miR-373 is abnormally expressed in a variety of tumor diseases and is closely related to cell biological behavior, it is clinically regarded as an important indicator for the early diagnosis, targeted therapy and prognostic monitoring of tumor diseases. In this paper, the regulatory mechanism of miR-373 in digestive tract tumors and other related research progress were comprehensively analyzed.

## Introduction

Malignant tumors have long been the focus of human medical research. The incidence and mortality of malignant tumors, especially tumors in the digestive tract, have significantly increased in recent years, as a result of changes in diet structure and living environment with the acceleration of the pace of life. Relative data show that [1,2] the incidence and mortality of digestive system malignant tumors ranks high globally, while gastric cancer, liver cancer, esophageal cancer, colorectal cancer and pancreatic cancer rank among the top ten. Although the incidence and mortality of malignant tumors have been reduced by multiple clinical treatments such as endoscopic therapy, radiotherapy, chemotherapy and targeted gene therapy. There is still a lack of ideal treatments and the mortality rate remains high. Recently, researchers have become increasingly aware of the importance of molecular variation in the evolution of tumor cells [3]. As a tool for studying molecular variation, gene mutation and epigenetics have begun to enter peoples' fields of vision. Epigenetics, such as hypomethylation of whole genome DNA and hypermethylation of specific genes, may result in the activation of oncogenes or the silencing of tumor suppressor genes, which in turn can lead to the development of tumors [4]. The epigenetic spectrum of cells consists of DNA methylation, histone modification, the regulation of non-coding RNA and chromatin remodeling. MicroRNAs are an evolutionary conserved noncoding small molecular RNA, and only a fraction of their biological functions have been specifically clarified at present. These miRNAs not only play an important role in the development and growth of the individual but are also essential to tissue expression, virus infection and protooncogene. Recently, multiple studies have concluded that miR-373 can promote the progression of malignant tumor diseases including prostate cancer [5], liver cancer and gastric cancer by functioning in proliferation, invasion and metastasis. Therefore, it is of great importance to consider miR-373 as a biological indicator for malignant tumor clinically, as well as a marker for targeted therapy and prognosis monitoring. Here, we reviewed the role

of miR-373 in digestive tract malignant tumors, and try to provide a theoretical foundation for digestive tract malignant tumors' treatment.

## Overview of the relationship between miR-373 and malignant tumor

### MiR-373 participate in the viral infection and inflammatory reaction of malignant tumor

Viral infection is an important pathogenic factor of diseases such as chronic hepatitis and liver cancer. The invading viral activates inflammatory reactions in the early stage of those diseases. With the gradual development of diseases, there will be an aggravated inflammatory reaction and pathological-state cells, eventually leading to the generation of malignant tumors. In gene therapy, miR-373 can activate system response and inhibit virus replication through targeting. MiRNA imbalance is one of the immune escape mechanisms for virus infection. MiR-373 could inhibit cell adhesion and promote cancer invasion in malignant tumor patients

### MiR-373 participate in cell proliferation, apoptosis, migration and invasion

Cell proliferation and apoptosis are important indicators of the occurrence and development of malignant tumors, while miR-373 is considered to be involved in those two processes. For example, miR-373 could change cell proliferation in the study of T-cell carcinoma [6], promote the proliferation and inhibit apoptosis of cancer cells in the renal cell carcinoma study [7]. The migration and invasion of malignant tumor cells are important cancer characteristics, which has a suggestive effect on the disease prognosis. For example, the mutation of miR-373 can inhibit the migration and invasion of cancer cells through targeting in lung cancer [8].

### As a biomarker for evaluating tumor diseases [2]

The abnormal expression of miR-373 was clinically tested in vitro, the abnormal expression of miR-373 indicates the occurrence, development and clinical characteristics of tumor diseases. In-depth clinical research on various cancers has concluded that miRNA is a good biological marker for non-invasive diagnosis.

## The role of miR-373 in digestive malignant tumor

### Liver cancer

Most patients have poor prognosis of hepatocellular carcinoma as there are no specific symptoms in the early stage until the time they got to the doctor, the cancer has often metastasized. The molecular mechanism of targeted metastasis is being studied clinically. Studies showed that miRNAs were abnormally expressed in hepatocellular carcinoma, and tissue examination was further carried out for solid tumors. The results showed that the expression of miR-373 was closely related to both cancer promotion and inhibition, and the expression of miR-373 varies from different tumors. For example, qRT-PCR was used to detect the transcription level of miR-373 in 96 cases of liver cancer tissues compared with normal liver tissues adjacent to cancer. Ye [9] found that the transcription level of miR-373 in liver cancer tissues was significantly lower than normal liver tissues adjacent to cancer. Moreover, Tao [10] further confirmed the opinion and also concluded that the low expression of miR-373 was highly related to the tumor size, vascular infiltration and poor prognosis of liver cancer patients. The overexpression of miR-373 could significantly inhibit the proliferation and the invasion of liver cancer cells, while the mutation of miR-373 had opposite effects. However, in the contrary, Lei [11] measured the expression of miR-373 in 80 hepatocellular carcinoma cases, and found that there was an up-regulated expression of miR-373 in those cases, which negatively correlated with tumor analysis. They further explored the role of miR-373 in liver cancer metastasis. After inhibiting miR-373 expression in HepG2 cell line, they found a significantly decreased migration and invasion ability of hepatocellular carcinoma.

### Gastric cancer

Gastric cancer is the most common malignant tumors, which characterized by a low early diagnosis rate, a high mortality rate and poor prognosis. MiRNA, as a recently used biomarker, is of great value in the tumor diagnosis and prognosis, which can be extensively involved in the tumor occurrence, development, and invasion. MiR-373 can directly increase the expression of transcription factor kB in the mutation of information regulator 2-related enzyme 1/ mammalian rapamycin target protein and enhance cancer cells' migration and invasion ability. Huang [12] further confirmed the result by studying 75 gastric cancer patients, and concluded that, miR-373 was highly expressed in gastric cancer patients compared with healthy people, the high expression of miR-373 also promoted the cancer progression. Further analysis of the clinicopathological characteristics of gastric cancer patients found the occurrence of worse differentiation of gastric cancer and a higher expression of miR-373 as the progression of disease. In Hu Guangjun's research [13], the miR-373 expression increased in gastric adenocarcinoma and gastric cancer cells, which confirmed the role of miR-373 in cancer promotion. Further analysis through fluorescein plum showed that miR-373 has a regulatory effect on the gastric cancer cells' transformation, the reducing expression of miR-373 can inhibit the cancer cells' migration and invasion. Reverse transcription quantitative polymerase chain reaction (Rt-qPCR) was used to compare the expression of miR-373 in clinical gastric cancer tissues and matched non-tumor tissues. The results [14] showed an increased level of miR-373 in gastric cancer compared with the matched non-tumor tissues. Also, the effects of miR-373 were studied on the proliferation, migration, and invasion of gastric cancer cells. It inhibits the migration and invasion of two gastric cancer cell lines, SGC-7901 and HGC-27, by decreasing vimentin expression, which proves the carcinogenesis of miR-373 in human gastric cancer metastasis.

### Esophageal cancer

Esophageal squamous cell carcinoma (ESCC) is a common tumor in the digestive tract. Clinical studies on the miRNA analysis of ESCC show a close relationship between various miRNAs and ESCC, for instance, a low expression of miR-29c and miR-205, a high expression of miR-10b, miR-483 and miR-64 was found in tumor tissues., Samples from 28 esophageal cancer patients were analyzed by RT-QPCR in Wu's study [15], along with the detection of 754 miRNA in serum and the characteristic curve of the subjects. The results showed an increasing expression of miR-25, miR-483-5p, miR-194, miR-337-5p, miR-223 and miR-

100, and they concluded that serum miRNAs could regulate 60% of gene expression and profile dynamic changes of malignant tumors. MiRNAs could degrade and inhibit translation with the combination of basic miRNA response elements, subsequentially regulate the process of cell proliferation, migration and differentiation. In the study of Chang Weidong [16], There is a lower serum miR-193b-3p expression of in esophageal squamous cell carcinoma than healthy controls, but showed a high serum miR-193b-3p expression after operation. Serum miR-373-3p is highly expressed in esophageal squamous cell carcinoma compared to healthy controls, while the level of serum miR-373-3p became lower after operation. The expression of serum miRNA is affected by the resection of cancer tissue. Liu Wenzhi [17] compared 63 Esophageal Squamous Cell Carcinoma (ESCC) patients with 39 healthy volunteers, and found that the expression of miR-373 significantly increased in ESCC tissue and peripheral blood, and the overexpression of miR-373 could promote cell proliferation, migration and invasion ability of ESCC. TIMP3, the direct target gene of miR-373, the inhibition of TIMP3 expression results in the increasing of tumor migration and invasion ability. Wei Wei [18] found that EIF3J-AS1 was up-regulated in esophageal cancer cells, and the high expression may correlate to an advanced TNM stage, invasion depth, positive lymph node metastasis and low survival rate. EIF3J-AS1/miR-373-3p/AKT1 formed a miRNA pathway involved in the molecular regulation of esophageal cancer cells. EIF3J-AS1 may elevate AKT1 mRNA level as an anti-molecular sponge of miR-373-3p, showing a carcinogenic effect in esophageal cancer. Based on above arguments, it is noted that miR-373, a biological detection marker of tumors, plays an important role in esophageal squamous carcinoma. The expression of miR-373 will promote the occurrence, development, and prognosis of the disease.

**Pancreatic cancer**

Pancreatic cancer characterized by a high risk of invading and metastasis. As a factor controlling gene expression, miRNAs have a significant impact on multicellular processes. For example, there is a low expression of miR-143 and miR-145 in pancreatic cancer. If the expression of those miRNAs is restored in tumor cells, the development of tumor will be inhibited. MiR-373 can inhibit the expression of CD44 and TGF-Br2 genes and decrease the migration and invasion of glioma cells. There was a significantly lower expression of miR-373 in pancreatic cancer compared with normal pancreatic cells in Nakata's study [19]. Also, the expression of miR-373 in pancreatic cancer samples was decreased after embedding in formaldehyde fixed paraffin and frozen. The expression of serum miR-629 of pancreatic cancer patients was promoted In Ma Wen's study [20], while the miR-373 expression was decreased. In addition, the level of miR-373 in blood was positively correlated with indicators including lymph node metastasis, tumor differentiation, distant metastasis and TNM staging. Thus, miR-373 mainly plays an inhibitory role to pancreatic cancer, while miR-629 may function in promoting pancreatic cancer. Moreover, Yin's research [21] showed that miR-373 can specifically target 3'-UTR of SIRT1 and reduce its expression in pancreatic cancer cells. The high expression of miR-373 or partial mutation of SIRT1 inhibits cell proliferation and induces cell apoptosis.

**Colorectal cancer**

Recent literatures reported that miR-373-3p is correlated with colorectal cancer. Tanaka's research [22] found that the abnormal methylation of miR-373-3p resulted in a decreased expression and the up-regulation of oncogene expression in colorectal cancer. Zhang [23] found that the down-regulation of miR-373-3p in ovarian cancer could inhibit the invasion and the migration of cancer cells. This view was concluded in Yang Xi's research [24] again, the results showed a decreased expression of miR-373-3p in colorectal cancer tissues, which means miR-373-3p had an inhibitory effect. In addition, the strain SW480 was transfected with Mimic of miR-373-3p. The results showed that miR-373-3p inhibited the expression of transcription protein---Rab22a, which showed a regulatory effect of mir-373-3p on Rab22a in colorectal cancer. Some researchers have concluded the contrary results. Wang [25] measured the expression of miR-372/373 of 607 colorectal cancer tissue samples and 11 adjacent normal colon tissues from TCGA. They found that miR-372/373 was not expressed in normal adjacent colon tissues but was highly expressed in colorectal cancer tissues. The overexpression of Wnt/-catenin signal, the downstream effector of miR-372/373, will enhances the stemness of colorectal cancer cells by targeting multiple genes/pathways involved in the differentiation and stem cell regulations. The pathological specimens from 150 patients after colon cancer surgery was studied by Ashoori H [26], they found that 32.6% of CRC patients had mutations of KRAS. Compared with patients without mutations, the expression of miR-31 and miR-373 were higher and has worse prognosis.

## Conclusion

In summerize, great progress has been made in miR-373 research especially in malignant tumors of digestive system. Many studies have concluded the close relationship between the expression of miR-373 and the tumor tissues including liver cancer, gastric cancer, esophageal cancer, pancreatic cancer and colorectal cancer. In the meantime, researchers also found that miR-373 is a faithful biological marker for the occurrence, development and prognosis of clinical malignant tumor, which is of great significance for the future diagnosis and treatment of relative diseases.

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