

Research Progress on the Role of miRNAs in the Development of Gastric Cancer

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Abstract

Gastric cancer is one of the most common malignant tumors in the world, with poor prognosis and is the main cause of cancer-related death. The 5-year survival rate of early gastric cancer can reach 90%. However, due to the low diagnosis rate of early gastric cancer, most patients are diagnosed as advanced gastric cancer at the first visit. Therefore, in order to improve the survival rate of gastric cancer patients, early diagnosis is particularly important. At present, tumor serum markers such as carcinoembryonic antigen (CEA), antibodies to Helicobacter pylori, histopathology, endoscopy, and determination of digested antigen are the main methods for the diagnosis and evaluation of gastric cancer. However, the effectiveness and sensitivity of these methods in the diagnosis of early gastric cancer are low. Therefore, it is of great significance to find new biomarkers with higher sensitivity and specificity for early diagnosis of gastric cancer. MiRNAs are abnormally expressed in many cancers, and some miRNAs are closely related to tumor development, progression and treatment. Therefore, miRNAs may be used as biomarkers for early diagnosis and prognosis of cancer in the future. In this review, the authors summarized the research progress of miRNAs in the development, early diagnosis and prognosis of gastric cancer, in order to provide new ideas for the future clinical treatment of gastric cancer.

Keywords

Gastric cancer, MiRNAs, Biomarker, Gene targets

Gastric cancer (GC) is one of the most common malignant diseases in the world. Although surgery, radiotherapy, chemotherapy and neoadjuvant therapy have made great progress, GC is still the third leading cause of cancer death in 2019 [1, 2]. The incidence of gastric cancer varies by region, with more than 70% of cases occurring in developing countries and more than 50% in East Asia [3]. Although chemotherapy and radiotherapy have extended the life of patients to a certain extent, an inevitable problem has emerged -- the resistance of tumor cells to chemicals or radiation limits the effectiveness of treatment, leading to poor prognosis, tumor metastasis and recurrence. Addressing this problem is a great challenge for cancer therapy, therefore, it is particularly important to find molecular markers for early diagnosis, prognosis and therapeutic targets of GC.

MiRNAs play an important role in cell apoptosis, proliferation, differentiation, tumor cell infiltration and other processes. The expression of miRNAs in different tumor tissues has a unique pattern, suggesting that there is a correlation between miRNAs expression and tumor progression [4-6]. The expression profile of miRNAs is correlated with tumor tissue type, suggesting the effectiveness of miRNAs as tumor clinical markers [7]. The unique expression profile of miRNAs in the plasma of cancer patients has been confirmed, indicating that they have certain potential in the diagnosis, treatment and prognosis prediction of cancer [8, 9].

1. Introduction to miRNAs

1.1 Structure and source of miRNAs

MiRNAs are post-transcriptional regulators of gene expression and are involved in almost all biological processes. MiRNAs are highly conserved small endogenous non-coding RNAs with a length of about 22 nucleotides, which play an important role in post-transcriptional gene regulation. By binding to complementary sequences in the 3' -untranslated region (3'-UTR) of various target mRNAs through site pairing with mRNA, miRNAs directly lead to mRNA degradation or translation inhibition. It inhibits gene expression by regulating mRNA stability and translation [10]. About 1% of genes in different organisms encode miRNAs. However, in mammals, it is expected that more than 60% of mRNAs are regulated by miRNAs [11].

1.2 Synthesis of miRNAs

The process of precursor miRNAs becoming mature miRNAs involves different biological steps [12]. When miRNAs are synthesized, miRNAs precursor genes are transcribed to form primary miRNAs (PRI- miRNAs) under the action of RNA polymerase II in the nucleus [13]. Pri-miRNAs are then cleaved into a stem-loop structure of about 85 nucleotides, called precursor miRNAs (pre-miRNAs), by a microprocessor complex consisting of RNA-binding protein DgCr8 and RNA polymerase III DROSHA [14]. After translocation of the Ran/GTP/Exportin 5 complex from the nucleus to the cytoplasm, precursor miRNAs are processed by another RNA polymerase III Dicer to double stranded miRNAs/miRNAs* of 20 to 22 nucleotides [15]. After double-strand unwinding, mature miRNAs are incorporated into a protein complex called RNA-induced silencing complex (RISC), which mediates gene silencing through mRNA cleavage and degradation or translational inhibition, depending on the complementarity between miRNAs and target mRNA transcripts [16]. In addition, miRNAs may act as ligands to directly bind Toll-like receptors (TLRS) and trigger downstream signaling pathways. Methyltransferase-like 3 (METTL3) is a recently identified gene that modifies PRI- miRNAs and marks them for recognition and processing by Dgcr8 to produce mature miRNAs.

2. The mechanism of miRNAs and gastric cancer

Under certain conditions, miRNAs can act as both oncogenes and tumor suppressors. Studies have shown that dysregulated miRNAs can influence tumor characteristics, including maintenance of proliferative signals, evasion of growth suppressors, resistance to cell death, activation of invasion and metastasis, and induction of angiogenesis. Oncogenic miRNAs, known as ONco-miRNAs, are usually upregulated in cancer and promote tumorigenesis and disease progression [17]. In contrast, "tumor suppressor" miRNAs inhibit tumor growth and are often downregulated in cancer. In fact, miRNAs have been implicated in various cancer-related processes, such as DNA damage response, differentiation, angiogenesis, aging, invasion and metastasis [18-23].

Mir-106a [24], Mir-21-5p [25], Mir-147 [26] and Mir-324-5p [27] inhibit proliferation and promote apoptosis of gastric cancer cells by directly targeting the tumor suppressor PTEN. Mir-21 [28], Mir-95-3p [29] and Mir-4295 [30] inhibit autophagy and regulate apoptosis-related proteins through PI3K/AK/MTOR signaling pathway. The expressions of Mir-126 [31], Mir-494 [32] and Mir-31 [33] are decreased in gastric cancer, and ZESTE gene enhancer homolog 2 (EZH2) is its target.

The expressions of Mir-129 [34], Mir-101 [35] and Mir-195-5p [36] are all down-regulated in gastric cancer, which can promote the chemotherapy sensitivity of GC cells by inhibiting the expression of P-glycoprotein (p-GP) in gastric cancer cells. Mir-140 [37] and Mir-647 [38] promote cell cycle arrest at G0/G1 phase. Mir-25 can promote the growth and inhibit the apoptosis of gastric cancer cells by targeting EGR2 and inhibiting EGR2 [39]. By targeting TIMP2, Mir-93 further elucidated the role of Mir-93 as a promoter in cell proliferation and metastasis in vitro and tumor formation in vivo [40]. Mir-200c [41] and Mir-338-5p [42] simultaneously target ZEB2 to regulate its expression in gastric cancer tissues. In prospective case studies, abnormally high expression of ZEB2 is positively correlated with more severe clinicopathology and worse survival.

Thus, various miRNAs can affect the occurrence and development of gastric cancer by acting on different target genes and signal transmission pathways in tumor cells.

3. MiRNAs and prognosis of gastric cancer

In the past few years, scientists have begun to investigate the possible role of miRNAs. Many studies have reported miRNAs expression profiles in human tumors to identify miRNAs associated with diagnosis, staging, pro-

gression, prognosis, and treatment response [43]. Fang et al. [44] proposed some oncogenic miRNAs (Mir-10b, Mir-21, Mir-223 and Mir-338) and tumor suppressor miRNAs (Mir-30a-5p, Mir-126 and let-7a) as prognostic signals in GC patients. The characteristics of miRNAs can be used to distinguish different types of cancer [45, 46]. Therefore, miRNAs can be used as clinical diagnostic and prognostic tools [47].

The up-regulation of Mir-191 and Mir-425 in serum of patients with advanced gastric cancer is an effective biomarker for the diagnosis, chemotherapy and prognosis evaluation of gastric cancer [48]. The expression of Mir-1915-3p is significantly correlated with lymph node metastasis and overall survival rate of gastric cancer patients, which may be involved in the occurrence and development of gastric cancer by inhibiting the anti-apoptotic protein Bcl-2 [49]. Mir-92a [50] and Mir-584 [51] can be effectively used as biomarkers to evaluate the diagnosis and prognosis of gastric cancer patients, as potential tumor markers for gastric cancer diagnosis, and as potential targets for gene therapy. Both Mir-17-5p and McL-1 increased in gastric cancer, and the prognosis and survival time of McL-1 high expression group decreased. These findings revealed a new regulatory signaling pathway of gastric cancer stem cells and provided new ideas for early diagnosis and molecular therapy of gastric cancer [52].

4. Prospects and challenges

Currently, detection of GC biomarkers is one of the major clinical challenges for researchers in gastric cancer due to poor prognosis, inadequate treatment options, resistance to chemotherapy or radiotherapy, and diagnostic lag. Therefore, the long-term goal of GC research is to find specific and reliable methods for early diagnosis and treatment of cancer [53, 54].

One of the greatest advantages of miRNAs for therapeutic use is that they can target multiple genes involved in similar pathways [55]. Restore normal cell cycle function by targeting miRNAs that inhibit normal cell cycle function. To further advance miRNAs in the field of cancer treatment, researchers are now exploring how to modify synthetic miRNAs so that they can be more easily transferred to host cells *in vivo*. By altering certain structural elements, such as the 2'-OH of ribose or the phosphate skeleton of synthetic miRNAs, the risk of their degradation by nucleases is reduced. The common approach to modify miRNAs synthesis is to package miRNAs in viral vectors, nanoparticles, or vectors containing miRNAs tandem repeats (antisense sponges), excluding host inflammation, proto-oncogene mutations, cytotoxicity, and high cost [56]. Changes in the level of a single miRNA can trigger a series of signaling events that ultimately lead to an overall increase or decrease in proliferation, apoptosis, and cell growth. MiRNA targeting strategy can implement precise treatment for cancer and play an important role in changing the progression and prognosis of the disease.

5. Subtotal

Gastric cancer specific miRNAs are involved in the occurrence and development of gastric cancer, and can also be used as the final diagnostic and prognostic markers of gastric cancer. In this review, the authors summarize the role of miRNAs dysregulation in the development of gastric cancer and the therapeutic role of identified targets in the past five years. The stability of circulating miRNAs offers the possibility of their suitability as diagnostic and prognostic markers for various cancers. With the in-depth study of these miRNAs and their target genes, it is expected that personalized treatment of gastric cancer will be implemented, opening up a new road for the treatment of gastric cancer.

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