Research Progress of circRNA in Epithelial Mesenchymal Transformation of Gastric Cancer

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Abstract

With the continuous progress in modern medicine, the early detection rate of gastric cancer has increased, and the mortality rate has decreased. However, gastric cancer remains the third leading cause of cancer-related death worldwide, with a high recurrence rate. Metastasis is the leading cause of death and recurrence of gastric cancer, which greatly hinders treatment success. Cancer development is a complex process involving multiple sequential steps. In the metastatic cascade, local invasion may be considered an initial, crucial step in the development of a malignant tumor, which leads to distant metastasis. Epithelial-mesenchymal transformation (EMT) is one of the most important developmental processes that occur during tumor invasion. EMT confers certain basic abilities to cancer cells, such as migration, invasion and anti-apoptotic ability, thus initiating and increasing metastasis. However, little is known about the molecular mechanisms that promote EMT and gastric cancer cell metastasis. A number of recent studies have found that circular RNAs（circRNAs）are associated with gastric

 doi:10.20944/preprints201908.0258.v1

cancer EMT, regulating the EMT process and promoting the occurrence and development of tumors. Because of their unique continuous circular structure, circRNAs have relatively high stability in plasma and cells, making them more suitable as diagnostic biomarkers in malignant tumors. Therefore, understanding the mechanism of circRNAs in EMT in gastric cancer is an important research direction to actively prevent tumor metastasis and improve the therapeutic effect on advanced malignant tumors.

Key words： circRNAs，gastric cancer，EMT

1.Introduction

Gastric cancer is one of the most common gastrointestinal malignancies in the world and the third leading cause of cancer death. In some western Asian countries, particularly in eastern Asia (including Japan, South Korea and China), the incidence has increased significantly[1]. The incidence of gastric cancer ranks third among all cancers in China, and the death rate ranks second among cancer-related deaths[2]. The 5-year survival rate for gastric cancer patients who are diagnosed early exceeds 90%[3]. However, due to the atypical clinical symptoms of patients with gastric cancer, early diagnosis is difficult, and the first diagnosis of most patients is in the late stage[4]. Moreover, in advanced cases, the treatment cost is high, and the benefit is small. The long-term prognosis of patients is not optimistic, and the 5-year overall survival rate is less than 30%[5]. The main cause of death and recurrence of gastric cancer is metastasis, which is the main obstacle in the clinical treatment of gastric cancer, accounting for the majority of the causes of

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gastric cancer death. Insufficient understanding of the molecular mechanism of the development and progression of gastric cancer is also a major problem in the diagnosis and treatment of gastric cancer. At present, the primary goal of gastric cancer research is to improve survival rates through early diagnosis and effective targeted therapy at various stages. Therefore, it is of great significance to study the molecular mechanisms of invasion and metastasis of gastric cancer, which also helps to identify new biomarkers for the diagnosis of gastric cancer patients.

Recent studies have found that epithelial-mesenchymal transition (EMT) is one of the key steps in the invasion and metastasis of gastric cancer. Among the numerous molecules and biochemical mechanisms involved in the EMT process, circular RNAs (circRNAs) are one of the important molecules. Recent studies have also shown that circRNAs are differentially expressed in a variety of human tumors and play an indispensable role in the pathogenesis of cancer[6-8]; that is, they play an important role in the occurrence and metastasis of cancer including gastric cancer[9, 10]. Therefore, this paper will review the progress on circRNA-related mechanisms in gastric cancer EMT.

1.Basic overview of EMT

In 1982, Greenberg and Hay first discovered the phenomenon of EMT in lens cells[11]. They found that lens epithelial cells could form pseudopodium in collagen gel and transform into mesenchymal cell-like morphology. Therefore, they defined EMT as the biological process of epithelial cells transforming from an epithelial phenotype to a dynamic mesenchymal phenotype under the action

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of specific pathological or physiological factors. EMT can be divided into three subtypes: type I EMT is related to embryonic development and also plays an important role in postnatal growth and development; type II EMT is stimulated by injury, and inflammatory repair is performed on damaged tissue, in which an aberrant repair process can cause damage to normal epithelial cells and organs; and type III EMT cells acquire interstitial invasion characteristics, which are related to metastasis and dissemination[12]. With further research, EMT has been gradually found to be closely related to pathophysiological processes such as embryo development, wound repair, tissue fibrosis, tumor invasion and metastasis, and tumor chemotherapy resistance[13, 14]. EMT is driven by the inhibition of epithelial-related genes (such as E-cadherin) and the activation of mesenchymal-related genes (such as fibroblast-specific protein 1 and vimentin)[12, 14, 15]. At present, the specific regulatory mechanism of EMT is still unclear. According to existing studies, signaling pathways such as TGF-β, Wnt/β-catenin, Notch, Hedgehog, IL-6/STAT3, and NF-κB can induce EMT processes. Important transcription factors involved in EMT are Snail1, Snail2, Twist1, Twist2, ZEB1, ZEB2, etc[16, 17]. In addition, recent studies have found that many noncoding RNAs (ncRNAs) are also involved in the regulation of tumor EMT, such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs)[18], and circRNAs have also been found to be important regulators of EMT[19, 20].

2. Basic overview of circRNA

CircRNAs were first discovered by Sanger et al. in plant viroids in 1976, and

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circRNAs were subsequently found in viruses and eukaryotes[21]. However, due to their low expression levels, circRNAs were considered a byproduct of false splicing and were not widely studies. As RNA research techniques develop, an increasing number of circRNAs have been found, whereby reverse repeat sequences, exon jumps, and RNA splicing have been shown to affect their formation[22], and circRNAs have been increasingly found to occur and develop in a variety of diseases[23, 24]. In particular, circRNAs play an important regulatory role in tumor development[25, 26], however their characterization in stomach cancer has just begun.

CircRNAs are endogenous ncRNAs that form a covalently closed continuous circular structure without 5' to 3' polarity or polyadenylated tail[27]. This structure makes circRNAs more stable in cells and not easily degradable by exonuclease. It is precisely because of their high conservation and stability that the diagnosis of malignant tumors by circRNAs will take precedence over other types of noncoding RNAs, which have great clinical potential to diagnose diseases. CircRNAs are produced by an exon, an intron, or intergenic splicing, and depending on their composition, are known as exon circRNAs, intron circRNAs, or exon-intron circRNAs. The biological functions of the currently known circRNAs include the following (Figure 1) [22, 28-31]: (1) regulation of gene transcription; (2) regulation of selective shearing; (3) regulation of the translation of parental genes; (4) regulation of the cell cycle; (5) sponge for some proteins; (6) miRNA sponge, blocking the inhibition of miRNAs on target

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genes; and (7) induction of the translation of n6-methyl adenosine (m6A).

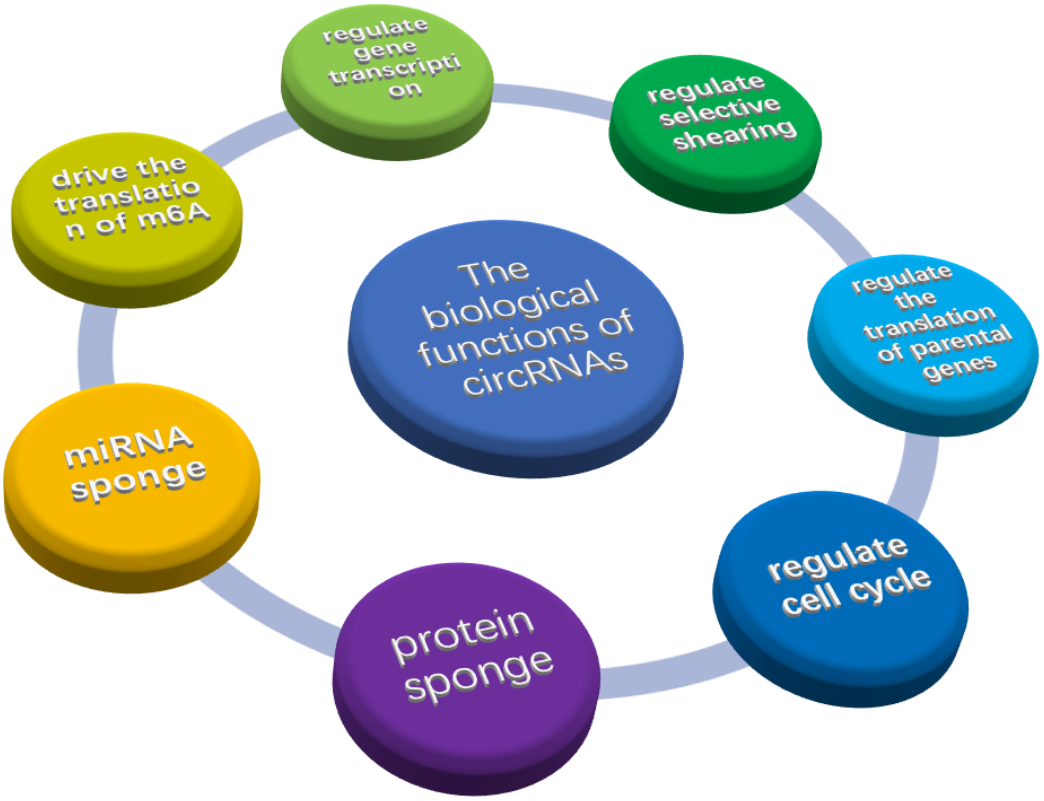

Figure 1: The biological functions of the currently known circRNAs

3. Study on the function of EMT in gastric cancer

With the help of bioinformatics analysis, circRNA chip analysis and high-throughput sequencing technology, numerous circRNAs have been found to be involved in the development of gastric cancer[20, 25]. CircRNA microarray analysis was performed in 6 patients with gastric cancer by Gu et al. to investigate the differences in circRNA expression between tumor and adjacent nontumor tissues[32]. They found that 440 circRNAs were expressed differently in tumor samples, including 176 upregulated circRNAs and 264 downregulated circRNAs. In another study[33], hsa_circ_0014717 was identified as the target circRNA. The global circRNA expression profile in human gastric cancer was

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measured by circRNA microarray, and the expression levels in gastric tissues and gastric juice were studied. A total of 308 circRNAs were found to be abnormally expressed in gastric cancer tissues, among which 107 were upregulated (34.74%) and 201 were downregulated (65.26%). Among the RNAs with differential expression, some circRNAs have been found to be related to the proliferation, invasion and metastasis of gastric cancer cells[34, 35]. Studies on the role of circRNAs in gastric cancer may provide new ideas for the diagnosis and treatment of gastric cancer. The recent discovery of circRNAs related to EMT in gastric cancer provides a new direction for the diagnosis and treatment of advanced gastric cancer.

As mentioned above, circRNAs have 7 different functions, among which, the regulation of gene expression as a miRNA sponge has been studied in most detail. Currently, there are 6 circRNAs found to be associated with EMT in gastric cancer, among which 3 have been found to play a role as miRNA sponges. Some are downregulated and act as tumor suppressors, while others are upregulated and act as oncogenes during carcinogenesis. Table 1 summarizes all of these circRNAs. CircCACTIN is upregulated in stomach cancer tissues and cell lines[10]. It affects the proliferation, migration, invasion and EMT of stomach cancer cells through a competing endogenous RNA (ceRNA) mechanism in the circCACTIN/miR-331-3p/TGFBR1 axis. In this study, the authors also found that circCACTIN and TGFBR1 had a consistent effect on cell phenotypes. As a result, circCACTIN is expected to become a new target for cancer treatment. Liang M et al[9]. showed a negative correlation between miR-195 and hsa_circ_006100 through bioinformatics analysis. Patients with high hsa_circ_006100 or low

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miR-195 levels had high TNM stages, poor cell differentiation, and lymph node metastasis. MiRNA-195 is targeted by hsa_circ_006100. Overexpression of hsa_circ_006100 enhances cell activity and proliferation and promotes the migration and invasion of MGC-803 and AGS cells. GPRC5A is predicted to be the target of miRNA-195 and is upregulated in stomach cancer. In vivo studies have shown that knockdown of hsa_circ_006100 delayed tumor growth, reduced PCNA expression and upregulated miR-195 and BCL-2 expression, which was restored by miR-195 inhibition via GPRC5A/EGFR signaling, and changed the EMT phenotype in vivo. It has been verified that circRNA-006100 is correlated with gastric cancer proliferation, invasion, EMT, etc. and may regulate the role of circRNAs in gastric cancer EMT through the miR-195/GPRC5A signaling pathway. Li et al. found that the ectopic expression of hsa_circ_104916 could effectively inhibit the proliferation, migration and invasion of gastric cancer cells in vitro, and during the EMT process[35], hsa_circ_104916 was shown to mediate an increase in the expression of epithelial molecules (E-cadherin) and a decrease in mesenchymal molecules (N-cadherin and vimentin) and a zinc finger transcription suppressor (SLUG). However, the exact mechanism by which hsa_circ_104916 regulates the expression of EMT-related molecules remains unclear. Similarly, the roles of circ_0009910 and circRNA_0023642 in the signaling pathway of gastric cancer EMT have not yet been identified. Precisely because the specific mechanism of circRNA involvement in the tumor EMT process has not been clearly studied, this may become a research direction of studies on tumor EMT in the next few years.

Table 1: Expression and effect of circRNAs in gastric cancer tissues and cells

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circRNA	References	Expression	Possible pathways	funtion
Circ_0009910	LIU M, LIU K-D, ZHANG L, et al.[36]	Up-regulated	needs further research	Proliferation, migration, invasion, and EMT
hsa_circ_0092303 （CIRCCACTIN）	Zhang L, Song X, Chen X, et al.[10]	Up-regulated	circCACTIN/miR-331-3p/TGFBR1 axis	Proliferation, migration, invasion, and EMT
hsa_circ_006100	M L, G H, Z L, et al.[9]	Up-regulated	miR-195/GPRC5A signal pathway	Proliferation, migration, invasion, apoptosis and EMT
circRNA_0023642	ZHOU L-H, YANG Y-C, ZHANG R-Y,	Up-regulated	demands for further research	Proliferation, migration,

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	WANG P et al. [37]			invasion, apoptosis and EMT
ciRS-7（CDR1as）	Hansen TB, Kjems J and Damgaard CK;[38]Zhao X, Dou W, He L, et al. [39]	Upregulated or Downregulated	ciRS-7/miR-7axis，insulin-like growth factor-1 receptor (IGF1R)	Proliferation, migration, invasion, apoptosis and EMT
circ-104916	J L, L Z, Y Z, et al.[35]	Down-regulated	needs further research	Proliferation, migration, invasion, and EMT

Conclusion

Studies have confirmed that peripheral invasion and distant metastasis are important causes of death in patients with gastric cancer. Currently, molecular biomarkers used in clinical practice have low organ specificity and low correlation with the clinical stage of cancer. For example, CEA is common in gastrointestinal tumors, while CA19-9 is more common in various adenocarcinomas. If circRNAs are used as biomarkers for gastric cancer in the clinic, their tissue-specific expression

 doi:10.20944/preprints201908.0258.v1

may help solve the problem of low organ specificity of existing markers and contribute to clinical prognosis. An increasing number of studies have demonstrated that EMT plays an important role in the migration and invasion of gastric cancer and that circRNAs also play a key role in digestive tract tumors. Therefore, understanding the regulatory effect of circRNAs on EMT and related molecular mechanisms can provide new ideas for the control of gastric cancer migration and invasion. However, compared with ncRNA, miRNA and lncRNA research, research on circRNAs in gastric cancer is still in its infancy. Although many functional circRNAs have been found and studied in gastric cancer, most studies have focused on the relationship between their expression level and pathological features. Studies on the relationship between circRNAs and EMT in gastric cancer are few and far between. The role of circRNAs in gastric cancer EMT still needs to be further confirmed by larger sample sizes, more data and cell experiments, and whether circRNAs can be truly applied in tumor diagnosis and treatment is still unknown. Further study on the regulatory mechanism of circRNAs in EMT will help reveal the mechanism of circRNAs in tumor metastasis and help find new targeted therapy strategies for EMT, which will have a profound impact on the improvement of the diagnosis and treatment of gastric cancer. In addition, how to efficiently transfer circRNAs or si-circRNAs to the exact lesion site without side effects is still a problem to be solved in clinical application. With the progress of molecular biology and bioinformatics technology, we hope to conduct more basic research on circRNAs, reveal the pathophysiological functions of circRNAs, develop circRNA-

 doi:10.20944/preprints201908.0258.v1

based treatment strategies, and integrate them into clinical practice safely and successfully.

Abbreviations:

EMT: Epithelial-mesenchymal transformation:

circRNA: Circular RNA

lncRNA: long noncoding RNA

miRNA: microRNA

ncRNA: noncoding RNA

ceRNA: endogenous RNA

Ethics declarations

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this paper. This study hadn't received any help from foundation or commence tissue.

Authors' contributions

Zhuoya Li wrote the paper and collected the data. Haojun Song convinced and designed the analysis. Xiaoyun Ding provided with valuable guidance in every stage of the writing of this thesis.

Acknowledgements

Not applicable

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