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Progress in Research Regarding Role of Circular RNA in Colorectal Cancer: A Review Article

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Abstract

Circular RNAs (Circ RNAs) are a group of endogenous non-coding RNAs (ncRNAs) which widespread in eukaryotic cells, and have been brought to the research hotspots recently. As a member of ncRNAs, Circ RNAs may play an important part in diseases by regulating target gene expressions, via epigenetic modifications. Colorectal Cancer (CRC) is a common malignant tumor worldwide, and its progress may be attributed to the dysfunctional expressions of target genes. Recent studies indicate that abnormal levels of Circ RNAs are detected in CRC cells, which may have a potential impact on this cancer. This review focus on the current understandings of the roles of Circ RNAs in CRC, with an aim to provide new aspects to the clinical diagnosis and therapy of CRC.

Introduction

Circular RNA (Circ RNA) is a special endogenous non coding RNA (nc RNA). Unlike linear RNAs, Circ RNAs do not have 5 'and 3' ends and form a closed circular structure with covalent bonds. Circ RNA was observed by Hsu et al. [1] in eukaryotic cells by electron microscopy as early as 1979. However, it has been considered as a by-product of RNA splicing process and has not attracted much attention. Recently, Salzman et al. [2] found a large number of Circ RNA expression in human cells, while Memczak et al. [3] identified more than 1000 Circ RNAs through RNA sequencing (RNA SEQ) and had great gene regulation potential. Colorectal Cancer (CRC) is one of the most common malignant tumors, and its incidence rate ranks the third among malignant tumors [4], showing an obvious upward trend, seriously threatening people's health. The development of CRC is affected by multiple factors such as genetics and environment, among which the abnormal gene expression of cancer cells plays an important role. As a member of nc RNA, Circ RNA has the potential to regulate genes on the basis of epigenetic modification, which may contribute to the exploration of the pathogenesis of CRC and is expected to become a new target

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for molecular diagnosis and treatment of CRC. In this paper, the characteristics of Circ RNA and its research progress in CRC will be reviewed.

Overview of circular RNA

Circ RNA formation

Circ RNAs are mainly sheared from precursor mRNA (pre mRNA) in two ways: exon cyclization and endon cyclization. Circular exon RNA mainly exists in the cytoplasm. Jeck et al. [5] proposed two cyclization models: lasso driven cyclization and intron pairing driven cyclization. Through exon skipping and intron pairing, the 3 'end of the downstream exon splicing donor of pre mRNA is inversely spliced to the 5' end of the upstream exon splicing acceptor. After the complementary bases of the introns on both sides are paired to form a nested lock, the introns are clipped to form a Circ RNA. These two cyclization models include long flanking introns containing Alu elements, which are easy to form complementation. Zhang et al. [6] recently demonstrated the cyclization model of intron driven pairing by enriching circrnas and adopting a new algorithm, that is, the cyclization of exon RNA depends on the complementary pairing of introns. Circular intron RNA (Circ RNA) mainly exists in the nucleus.

Zhang et al. [7] proposed an intron self cyclization model, which can generate Circ RNAs only from introns. Li et al. [8] recently discovered exon intron circrnas (exon intron Circ RNAs, eicircrnas) that contain both exon and intron sources, and the formation mechanism is still unclear.

Biological characteristics of circrna

Current studies have shown that Circ RNAs have the following remarkable biological characteristics: (1) they are numerous and widely distributed in eukaryotic cells [2,5]. (2) It is stable in nature and is not easily recognized and hydrolyzed by RNA ribonuclease r due to its lack of 5 '- 3' polarity [9]. (3) It has spatiotemporal specificity [2, 3], and is expected to become a new generation of diagnostic markers. (4) It has biological evolutionary conservation [2,5].

Abnormal expression of circular RNA in colorectal cancer

The occurrence and development of CRC are closely related to the abnormal changes of genes. The changes include not only modifications at the gene level, but also modifications at the epigenetic level, that is, changes in the expression of microRNAs (miRNAs) [10]. Circ RNA is also a potential material for regulating target genes. It is very important to explore the expression difference between tumor tissues and normal tissues.

Down regulation of Circ RNA expression in CRC

Some Circ RNAs were down regulated in CRC, suggesting that there might be tumor suppressive effect. Bachmayr et al. [11] selected 12 pairs of CRC tissues and normal colon specimens and sequenced 85 Circ RNAs by RNA SEQ technology, of which 73.4% were low, expressed in cancer tissues. In order to further confirm, 31 pairs of colon cancer clinical specimens and 11 pairs of colon cancer cell lines were selected, and four Circ RNAs were detected by real-time quantitative polymerase chain reaction (RT qPCR) and their corresponding parental linear RNAs. Compared with normal colon mucosa, the overall expression level of circrna in colon cancer tissues and colon cancer cell lines was low. It suggests that some Circ RNAs may be negatively correlated with tumor cell proliferation. Wang et al. [12] recently selected CIRC-001988, 31 pairs of CRC tissue and normal tissue samples were analyzed by RT qPCR, and CIRC-001988 was significantly under expressed in CRC tissues and was significantly correlated with CRC tissue differentiation and perineural invasion. Huang et al. [13] found in the study of 45 pairs of CRC tissues and their adjacent normal tissue samples that the expression of CIR itch was abnormal and significantly down regulated in CRC specimens.

Up regulation of Circ RNA expression in CRC

Some Circ RNAs are up regulated in CRC, suggesting that they may participate in the tumor promoting effect. Xie et al. [14] selected CIRC-001569, RT qPCR was used to analyze 30 pairs of CRC clinical specimens and found that CIRC-001569 expression level of 001569 was significantly higher in CRC tissues than in surrounding normal tissues, and its expression was closely related to CRC differentiation and TNM stage. It further selected CRC cell line for analysis and found that CIRC- 001569 promotes the proliferation and invasion of cancer cells. Recently, Zheng et al. [15] transfected small interfering RNA (siRNA) into colon cancer cell lines, targeted knockdown reduced the expression of CIRC-HIPk3, and found that it could significantly inhibit the proliferation of tumor cells, indicating that CIRC-HIPK3 has a certain tumor promoting effect. Through RT qPCR, Weng et al. [16] found that the expression of Cirs-7 in CRC cell lines was significantly up regulated, and it up regulated the expression of Epidermal Growth Factor Receptor (EGFR) and oncogene Raf1, playing an obvious tumor promoting effect.

Circular RNA micro RNA colorectal cancer regulatory axis

miRNAs belong to a class of small ncRNAs composed of only 18-25 nucleotides, which can usually regulate genes by targeting epigenetic complexes such as DNA or histone modifying enzymes [17]. Many studies have shown that some miRNAs, such as miR-143 and miR-145, as tumor suppressor genes, affect CRC tumor proliferation [18-21]. However, recent studies have found that some Circ RNA s contain many binding sites of miRNAs, which can act as miRNA sponges, that is, through complementary pairing of binding sites, competitively adsorb miRNAs, affect the binding of miRNAs to their target mRNAs, and thus affect the function of gene expression [3,22]. It means that Circ RNA s may act as miRNA sponges in the process of regulating CRC, and regulate CRC tumor development through Circ RNA miRNA CRC regulatory axis.

Cirs-7 is a Circ RNA transcribed by the antisense strand of brain degradation related protein 1 (CDR1), also known as cdr1as. It is one of the research hotspots of Circ RNA. The surface of Cirs-7 contains more than 70 binding sites of miR-7, which can act as a miR-7 sponge, efficiently adsorb miR-7, limit its silencing effect on target gene mRNA, and promote the expression of oncogenes (such as EGFR) [22-24]. However, Zhang et al. [25] found that miR-7 was down regulated in CRC cell lines and had the function of tumor suppression. It inhibits the growth of CRC tumors by negatively regulating the expression of oncogene YY1 (Yin Yang 1). The above studies indicate that cirs-7 may play an important role in promoting the growth of CRC tumors by acting as a sponge of miR-7. However, few studies have directly explored the relationship between Cirs-7 and CRC. Recently, Weng et al. [16] found that Cirs-7 can be a new oncogene of CRC, and its expression is up-regulated in CRC tissues, and it plays a tumor promoting effect by inhibiting the function of miR-7. In addition, Xie et al [14] found that Circ RNAs-001569 was significantly up regulated in CRC, and as

a sponge of miR-145, it suppressed the silencing effect of miR-145 on its target genes, thus promoting the proliferation and invasiveness of CRC tumors. Zheng et al. [15] found that Circhipk3 contains binding sites of 9 miRNAs through luciferase detection reagent, which can act as a sponge of these miRNAs and exert tumor promoting effect. Among them, the effect as miR-124 sponge is the most obvious. Therefore, the upregulation of Circ RNA expression in CRC may play a tumor promoting effect on CRC through Circ RNA miRNA regulatory axis.

However, at the same time, miRNA sponge effect was also found in the study of down regulation of Circ RNA expression. Huang et al. [13] found that the expression of CIRC ITCH was significantly down regulated in CRC specimens, and found that both CIRC ITCH and its parent gene ITCH had binding sites of miR-7 and miR-20a, and further found that miR-7 and miR-20a could bind itch and down regulate the expression of ITCH. Since CIRC ITCH competitively adsorbed miR-7 and miR-20a, it indirectly up regulated ITCH, while ITCH could block Wnt/β- Catenin pathway, inhibiting tumor proliferation. Therefore, CIRC RNA miRNA regulatory axis may also indirectly exert its anti-tumor effect on CRC. However, the specific mechanism of the tumor suppressive effect of other Circ RNAs on CRC needs further study. At present, tens of thousands of Circ RNAs have been found to have the function of miRNA sponge [26], they may all have the potential to regulate CRC and may become new oncogenes or tumor markers. However, there are too few validation studies and insufficient evidence. The miRNA sponge effect of Circ RNA s needs further exploration.

Clinical application prospect of circular RNA

Circ RNA may become a new diagnostic marker for CRC and a follow-up indicator for disease progression and prognosis. Firstly, some Circ RNAs are significantly differentially expressed in CRC tissues and surrounding adjacent tissues. Shao Jingxian et al. [27] screened Circ RNAs in 6 pairs of human CRC tissues and surrounding normal tissues through high-throughput Circ RNA chip technology and found that 892 Circ RNAs are differentially expressed, including 412 highly expressed and 480 low expressed in CRC tissues. These differentially expressed Circ RNAs may become new targets for clinical diagnosis. Secondly, the nature of Circ RNA is more stable than that of linear RNA. It is a closed loop and does not contain 3 'and 5' ends. It is difficult to be recognized and hydrolyzed by RNA ribonuclease R, which is conducive to stable expression and maintenance in cells and purification during experimental analysis [28]. Finally, Circ RNAs are also highly stable in the extracellular and blood circulation, and only a small amount of blood [29] is required to detect Circ RNAs. Recently, it was found that the expression of a variety of circrnas was detected by enriching the exosomes of blood samples from CRC patients, and verified by RT qPCR, which proved that Circ RNAs also exist stably in exosomes [30], laying a theoretical foundation for practical clinical testing.

Circ RNA is also expected to become a new therapeutic target. Because some Circ RNAs can be used as miRNA sponges, they have more miRNA binding sites and are more effective than traditional linear miRNA sponges. For miRNAs with tumor promoting effects, Circ RNAs can play a potential therapeutic role as more effective miRNA inhibitors. For miRNAs with tumor suppressive effect, Circ RNAs can be negatively regulated by introducing other miRNAs to compete for targeted inhibition of Circ RNAs. For example, Hansen et al. [31] found that mir-671 can fully complement and bind with cirs-7 and guide its degradation, so it can indirectly enhance the anti-cancer effect of miR-7. However, not all Circ RNAs can be used as miRNA sponges, and the regulatory mechanism of some Circ RNAs on tumors needs further study.

Conclusion

Circ RNA is another new research hotspot in the field of ncRNA research after miRNA and long non coding RNA (lnc RNA). Because of its abnormal expression in CRC tumor tissues and its own stability, it may become a new CRC tumor marker or therapeutic target. At present, some studies have successfully constructed artificial Circ RNAs or regulatory interference endogenous Circ RNAs [32], laying a theoretical foundation for its clinical application. It is believed that its application in early diagnosis, targeted treatment and prognosis evaluation of CRC still has a huge space and can become a sharp edge against CRC tumors. However, there are few studies on the regulatory mechanism of Circ RNAs on CRC, and there are more studies on the relationship between Circ RNAs and CRC.

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