

Review Article

Circular RNA (CircRNA) and YAP in tumor: A review

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Abstract: Background: Circular Ribonucleic Acid (circRNA) is a type of RNA that has been found in recent years and is a closed loop structure widely found in eukaryotic cells. **Present situation:** The circRNA is stable in nature, highly conserved and tissue and disease specific, and regulates target gene expression at the transcriptional or posttranscriptional level, which is related to the occurrence and development of tumors. YAP (Yes-associated protein) is the main effector of Hippo signaling pathway. It is found that YAP level is closely related to cell proliferation and apoptosis, tissue organ size control and tumorigenesis. **Aim:** to study the correlation between circRNA and YAP in tumors.

Keywords: Tumor; circRNA; YAP

1. Introduction of circRNA

Ring RNA is a kind of RNA that does not have a 5 terminal cap and a 3 terminal poly (A) tail and forms a closed ring structure by covalent bonds, mostly non-coding RNA. Because of its structural characteristics, circRNA is stable to nucleic acid exonuclease and has high conservativeness and tissue, space-time and disease specificity^[1-3]. CircRNA widely exists in cells. Genomic research shows that there are more than 100,000 kinds of circRNA in human cells. In human fibroblasts, the content of circRNA quantity is 10 times of linear RNA (linear RNA CircRNA plays a regulatory role mainly through adsorption of miRNA ,regulation of transcription, binding of proteins, translation and splicing and other 5 aspects^[4-10]. Previous studies have found that cyclic RNA is diseases (such as cardiovascular diseases^[11], Alzheimer's disease^[12,13], Parkinson's disease^[14] etc.) and tumors (such as esophageal cancer^[15], gastric cancer^[16], liver cancer^[17], colon cancer^[18] etc.) play important roles.

2. Formation and classification of circRNA

CircRNA was first believed to be caused by RNA splicing errors^[19]. However, with the deepening of research and the development of RNA sequencing technology, more and more studies show that the splicing mechanism of circRNA is complex, and circRNA may be generated in any region of the genome sequence, and different types of circRNA^[20,21] may be generated at the same gene site. According to different splicing sources, circRNA can be divided into circRNA (exonic circular RNA), ecircRNA ,and circRNA (circular intronic RNA), ciRNA, intron sequence and explicit in the form of intron sequence. Circ RNA formed by subsequences (Exon-intron Circ RNA, EIciRNA) and Circ RNA (tRNA

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in tronic Circ RNA, tricRNA) formed by splicing the introns of RNA (Transfer Ribonucleic Acid, tRNA) through Trna precursor. EcircRNA can be composed of one or more exon sequences, mainly existing in cytoplasm, while intron loop RNA mainly distributed in nucleus^[22,23]. EcircRNA is made up of linear RNA through exon skipping during transcription, 3 end-cutting donor and 5 end-cutting receptor binding to produce a noose containing exons. The intron is then excised to form. The formation of ciRNA is different from that of ecircRNA. The sequence capable of forming ciRNAs requires GU enrichment element at 5 shear site and C enrichment element at 3 shear site. In the process of reverse shearing, the 2 segments are paired with each other to form a ring structure. After that, the excimer excises the redundant exon and intron sequences in the sequence, and the remaining introns form icircRNA^[24]. EIciRNAs are formed by base pairing between introns, pre-mRNA shear splicing. When more than one exon is cyclized, if the intron sequence is retained, both exons and exons will be formed. intron EIciRNA^[24]. TricRNA is formed by splicing tRNA introns through tRNA precursors^[24,25].

3. Function and regulation mechanism of circRNA

3.1 CircRNA interacts with miRNA

MiRNA (MicroRNA) is a regulatory non-coding RNA(Non-coding RNA) and ncRNA commonly existing in organisms. They usually inhibit the expression of target genes at post-transcriptional level^[25]. Most circRNA Contains miRNA Reactors pieces (microRNA response element, MRE) are used to bind specific miRNA. Therefore, circRNA can be used as highly competitive endogenous RNA (competitive endogenous RNA, ceRNA) to remove the inhibitory effect of miRNA on target genes by adsorbing miRNA. Therefore, studying the sponge effect of miRNA of circRNA may explain the molecular mechanism of some diseases. Cerebellar Degeneration Associated Protein 1 Antisense Transcript (Circnacirs-7/CDR1as) is the first miRNA to be discovered circRNA that regulates gene expression through spongy action. CDR1as is produced by cdr1 gene in reverse shear. It miRNA binding sites, which play a negative regulatory role on miR-7. When CDR1as is overexpressed, the expression level of miR-7 target gene will increase. On the contrary, when CDR1as is inhibited, the expression level of miR-7 target gene will decrease^[26]. Research^[20] shows that miR-7 can regulate some key proteins of tumor-related signaling pathways, such as Epidermal growth factor receptor (EGFR), EGFR), insulin receptor substrate I and substrate II, p21 protein activated kinase I (protein activated kinase I, Pak1), activated CDC42 kinase I (activated CDC 42 kinase I, Ack1) and the like are used as cancer inhibiting factors to inhibit proliferation activity and invasiveness of glioma cells, breast cancer cells, gastric cancer cells and the like. Testicular specificity circRNA containing 16 miR-138 binding sites^[6] related to sex-determining region Y (sex-determining region Y, Sry) gene can interact with miR-138 to regulate the expression of miR-138 target gene. In addition, Tian Fang *et al.*^[27] reported that circular RNA CircHIPK3 (circular RNA HIPK3 can bind miR-379 and regulate the expression of insulin-like growth factor (IGF1) to promote cell proliferation.

3.2 CircRNA interacts with proteins

CircRNA can directly bind proteins or couple RNA binding proteins (RNA-binding protein, RBP) to participate in the regulation of various physiological processes. Studies^[28] found that high-level Circ-FoxO3 (Circ-FoxO3) can form Circ-FoxO3-p21-CDK2 triplet complex from egg white P21 and CDK2 (Cyclin-Dependent Kinase-2) in the perikaryocytic phase of normal cells. CDK2 can weaken the cell proliferation ability, so it is believed that circ-Foxo3 can promote the cell proliferation and cycle of tumor cells through this form. In addition, circ-Foxo3 can also regulate the corresponding resistance process through interaction with proteins such as focal adhesion kinase, FAK and human hypoxia inducible factor 1 α (hypoxia inducible factor 1 α , HIF1 α) Hascirc0024707 has multiple RBP binding sites and can be used as a competitive element to regulate the function of RBP. It has an effect on biological processes such as shearing, transcription and translation, cell proliferation, differentiation and aging that RBP may participate in CircRNA. The interaction between molecules and proteins can also be used in the treatment of diseases. Bohjanen *et al.*^[29] designed a circRNA molecule capable of specifically binding to trans-activating regulatory protein, Tat to inhibit the

expression of human immune deficiency virus type 1, HIV-1 gene.

3.3 CircRNA's translation function

Recent studies have found that some circRNA can be translated into proteins under certain conditions. CircRNA in cytoplasm can also participate in protein translation once the internal ribosome entry site is activated. For example, hepatitis D virus, HDV circRNA whose core contains a single negative strand covalently closed can be translated into HDV antigen^[20]. Wang *et al.*^[30] reverse shear simulates circRNA before constructing the internal ribosome access site (internal ribosome entry site, IRES) to the Open reading frame (Open Reading Frame, ORF) of Green fluorescent protein (Green Fluorescent Protein, GFP), and this simulated circRNA has translation function. Another study^[31] believes that circRNA with complete RNA translation elements such as ORF, IRES and N6, methyl adenosine (N⁶-methyl adenosine, m⁶A etc.) may be translated into peptide fragments. Yang *et al.*^[10] found that m⁶a can recognize YTH domain family protein 3 (YTH domain family protein3, YTHDF3) and can bind to the modification site of circRNA, and drive the translation of circRNA by raising eukaryotic translation initiation factor (eukaryotic translation initiation factor, eIF4G2) and other translation initiation factors; In addition, a large amount of circRNA combined with polysomes may be evidence of its translation function.

3.4 CircRNA regulates expression of parent genes

Studies^[20] show that circRNA can regulate the transcription of parent genes and affect the expression of parent genes and their target genes. Some cells contain rich circRNA in their nuclei, which promotes transcription of coding genes through interaction with polymerase II. Anchor protein repeat domain 52 (ci-ankyrin repeat domain 52, ci-ankrd52), as a positive regulator of polymerase II complex, aggregates transcription sites of its own coding genes, can positively regulate transcription activity of RNA polymerase II complex, and plays cis-regulatory role on matrilineal genes^[32]. CircRNA can also regulate the stability of mature mRNA. Some circRNA also has the function of protecting cells from invasion of exogenous pathogens. For example, after knocking out the expression of mcircRasGEF1B (a kind of lipopolysaccharide-induced circRNA), the expression of lipopolysaccharide-induced intercellular adhesion molecule -1 will also decrease to protect cells from infection by exogenous pathogens^[33].

3.5 CircRNA research progress in cancer

CircRNA is a new non-coding RNA and plays an important role in cancer. With the development of microarray chips and next generation sequencing technology, many circRNA have been detected or identified in cancer samples. Adenocarcinoma of pancreatic duct has been confirmed.

The expression profile of circRNA in the early stage of (Pancreatic ductal adenocarcinoma, PDAC) reveals that dysfunctional circRNA may be involved in the progress of PDAC and may be used as a new therapeutic biomarker^[34,35]. In another study, microarray analysis also showed that circRNA_100855 and circRNA_104912 are the most significantly misaligned circRNA in laryngeal cancer tissue, while circRNA_001059 and circRNA_000167 are significantly misaligned in radiation-resistant esophageal cancer^[36,37]. In colorectal cancer, 379 dysregulated circRNA^[38] were identified using Circ RNA microarray analysis. In glioma, RNA-Seq data show that there are more than 476 species of misaligned circRNA^[39]. A recent study identified circRNA^[40] associated with breast cancer subtypes using Circ-Seq. In addition, the expression profile of circRNA in KRAS mutant colon cancer is identified by RNA-Seq data^[41]. Interestingly, by combining microarray circRNA expression profile with bioinformatics target prediction and sequence analysis, it has been applied to Basal cell carcinoma (Basal Cell Carcinoma, BBC) and skin squamous cell carcinoma. Many circRNA^[42,43] with MRE disorder have been identified in ("cutaneous squamous cell carcinoma, CSCC"). Recently, it is reported that 69 kinds of differentially expressed circRNA may interact with some miRNA and affect the mRNA expression^[44] in gastric cancer (Gastric Cancer, GC) Genwen Chen's research shows that circRNA_100782 is significantly up-regulated in PDAC tissue. Functional experiments show that circRNA_100782 down-regulates and inhibits cell proliferation and colony formation of pancreatic ductal adenocarcinoma BxPC3.

Functional loss research shows that, Knock down circRNA_100782 By Down-regulating miR-124 Target Gene Interleukin -6 Receptor (Interleukin-6 receptor), IL6R) and Signal Transducer and Activator of Transcription 3 (Signal Transducer and Activator of Transcription 3, STAT3) to inhibit cell proliferation. In short, CircRNA_100782 regulates pancreatic cancer proliferation through IL6-STAT3 pathway^[45]. Studies have confirmed that circRNA is differentially expressed in lung squamous cell carcinoma (Squamous cell carcinoma of the lung, LSCC) and is closely related to carcinogenesis of LSCC. Among them, HSA _ CIRC RNA _ 103827 and HSA _ CIRC RNA _ 000122 can be used as potential prognostic biomarkers and therapeutic targets for LSCC^[46]. In addition, studies have confirmed that circRNA_0000285 may be a new biomarker of Nasopharyngeal carcinoma (NPC) and participate in NPC radiosensitivity^[47]. The above conclusions all confirm the important regulatory role of circRNA in cancer, but the overall mechanism of circRNA in cancer has not been fully clarified.

4. YAP and circRNA correlation study in tumor

Hippo Pathway plays a prominent and extensive role in various forms of human cancer. Especially YAP, Hippo. The downstream effector of the pathway can cause excessive cell proliferation and inhibition of cell apoptosis, leading to tumorigenesis. It is reported that the expression of YAP is significantly increased in various types of human malignant tumors, such as breast cancer, lung cancer, small intestinal cancer, colon cancer and liver cancer^[48]. Clinicopathological and biological results show that the increase in activation and expression of YAP is related to tumor staging and prognosis^[49-55]. Therefore, we believe that YAP as a potential oncogene is a promising independent prognostic biomarker for various cancers. Liu G^[56] *et al.* circFAT1 derived from fat1 gene exon 2 in human osteosarcoma (osteosarcoma) tissues and cell lines was significantly up-regulated. Inhibiting circFAT1 can effectively prevent osteosarcoma cells from migrating, invading and tumorigenesis in vitro and inhibit osteosarcoma growth in vivo. Mechanism research shows that circFAT1 contains miR-375 binding sites, which can bind a large number of miR-375 up-regulate the expression of YAP. In addition, the inhibition of miR-375 reverses the attenuation of cell proliferation, migration and invasion induced by knockout of circFAT1, thus promoting the occurrence of tumor. Lorena Verduci^[57] and other studies have found that compared with matched non-tumor tissues, circPVT1 is overexpressed in tumor tissues of patients with head and neck squamous cell carcinoma (Head and Neck Squamous Cell Carcinoma, HNSCC), especially the enrichment of TP53 mutant patients. CircPVT1 up-regulation and down-regulation determine the increase and decrease of malignant phenotype in HNSCC cell line respectively. At the same time, it is proved that circPVT1 is expressed through MUT-p53 (mutantp53 proteins)/YAP/TEAD (TEADOMAIN) complex transcription enhancement. CircPVT1 acts as an oncogene to regulate the expression of miR-497-5p and genes involved in controlling cell proliferation. Xiao Zhang^[58] *et al.* found that circRNA_104075 is highly expressed in liver cancer tissues, cell lines and serum. Mechanically, hepatocyte nuclear factor HNF4A (Hepatocyte nuclear factors 4A) binds to region 1409-1401 of promoter circ_104075, stimulating expression of circ_104075. Circ_104075 acts as ceRNA up-regulates YAP expression by absorbing miR-582-3p. Interestingly, the M 6 A motif was found in the 353-357 region of YAP 3UTR. This m⁶A modification is essential to the interaction between miR-582-3p and YAP 3UTR. The diagnostic performance of circ_104075 was evaluated. Circ_104075 the area under the subject's working characteristics (the area under the receiver operating characteristic, AUC-ROC) is 0.973, the sensitivity is 96.0%, and the specificity is 98.3%. In short, we determined that circ_104075 is highly expressed in hepatocellular carcinoma, and clarified its upstream and downstream regulatory mechanisms. In addition, circ_104075 also has potential as a biomarker for liver cancer diagnosis. Targeted circ_104075 May Provide New Strategies for Diagnosis and Treatment of Hepatocellular Carcinoma. Jianhua Zhang^[59] *et al.* Studies have found that circRNA hsa_circ_0023404 is significantly higher in Cervical cancer (CC) tissues than adjacent normal tissues. Its overexpression is associated with poor prognosis of CC patients. Functionally, hsa_circ_0023404 knockout significantly inhibits CC cell proliferation, inhibits cell cycle process, and inhibits cell migration and invasion. In terms of mechanism, hsa_circ_0023404 serves as a sponge for miR-136 and miR-136 targeting TFCP2 and is an activator of YAP signal pathway. Hsa_circ_0023404 Promotes TFCP2

Expression through Sponge Action miR-136 Activates YAP Pathway in CC, thus Leading to Development and Progress of CC. Zhen Liu^[60] *et al.* performed circRNA microarray analysis on RNA extracted from cells treated with or without YAP1 SiRNA (Small Interfering RNA) showed that circRNA-000425 was Yap1 target, and passed RT-qPCR.

The determination of real-time quantitative reverse transcription-polymer chain reaction and chip (chromatin immuno prediction) further confirmed. Interestingly, bioinformatics analysis, luciferase assay and RT-qPCR results show that circRNA-000425 binds to miR17 and miR-106b, but does not bind to let-7a, and reduces the inhibitory effect of miR-17/miR-106 on the expression of p21 and BIM (bcl-2 interacting mediator of cell death). In addition, methods such as colony formation and MTT metabolic activity assay show that circRNA-000425 inhibits cancer cell growth induced by miR-17. These findings reveal the mechanism by which YAP1 inhibits the carcinogenic activity of circRNA-000425 promotes miR-17 and miR106b through transcription.

5. Conclusion

To sum up, previous studies have shown that there are many kinds of circRNA and YAP that interact with each other and play a role in the occurrence and development of tumors. Due to the structural stability and functional diversity of circRNA and the important role of YAP in cell proliferation, apoptosis and other processes, joint research on the potential clinical value of circRNA and YAP in tumor diagnosis, treatment and prognosis is of great significance.

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