Biological Roles of circRNAs

Subjects: Cell Biology

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Circular RNAs (circRNAs) comprise a large class of endogenous non-coding RNA with covalently closed loops and have independent functions as linear transcripts transcribed from identical genes. circRNAs are generated by a “back-splicing” process regulated by regulatory elements in cis and associating proteins in trans. Many studies have shown that circRNAs play important roles in multiple processes, including splicing, transcription, chromatin modification, miRNA sponges, and protein decoys. circRNAs are highly stable because of their closed ring structure, which prevents them from degradation by exonucleases, and are more abundant in terminally differentiated cells, such as brains.

Keywords: circRNA ; biomarker ; therapeutic target

1. Introduction

Covalently closed circular RNAs (circRNAs) are a large class of non-coding RNAs that are generated by a process called back-splicing. In 1976, the first circular RNA molecule (viroid) was discovered as a pathogen by Sanger sequencing [1]. After a few years, Hsu et al. [2] reported the presence of the circular form of RNA in the cytoplasmic extraction of several eukaryotic cells using electron microscopy. Since then, a variety of circular RNAs have been reported. In 1991, Nigro et al. discovered some abnormally spliced transcripts called “scrambled exons”, which originated from the candidate tumor suppressor gene *deleted in colorectal cancer* (*DCC*) and were produced by non-canonical splicing [3]. A year later, similar transcripts from the human *ETS proto-oncogene 1, transcription factor* (*ETS-1*) gene were reported [4]. In 1993, Cocquerelle et al. identified that these mis-splicing products from the *ETS-1* and *DCC* genes are circular RNA molecules containing only normally spliced exons and are localized in the cytoplasm [5]. The second report in 1993 demonstrated that the *Sry* RNA molecules in cDNA and 5′RACE clones isolated from mouse testes have a circular structure [6]. This circular RNA represents the most abundant transcript in the cytoplasm and testis, indicating that it might be functional. Several other studies have documented that exon circularization can be induced in nuclear extracts in vitro [7][8]. In recent years, the advancement of high-throughput RNA sequencing (RNA-seq) followed by bioinformatic algorithms specialized for circRNAs has identified thousands of circRNAs in metazoans, including *Drosophila*, nematodes, mice, and humans, and have shown their tissue- and developmental-specific expression pattern [9][10][11][12][13][14].

Most circRNAs are generated by back-splicing, in which a downstream splice donor site is covalently linked to an upstream splice-acceptor site, and are abundant in the cytoplasm. Bioinformatic algorithms that identified circRNAs from long-read RNA-seq data revealed that more than half of the circRNAs span <5 complete exons and consist of only protein-coding exons, especially in 5′-untranslated regions (UTRs) [15]. In contrast to exon-derived circRNAs, failure in intron lariat debranching or internal intron retention during canonical splicing may produce circular intronic RNAs (ciRNAs) and exon–intron circular RNAs (EIciRNAs), respectively. These classes of circRNAs are abundant in the nucleus and act as stimulators of the transcription of their parental genes in cis [16][17].

In general, circRNAs are highly stable because of the covalently closed ring structure that protects them from degradation by exonucleases [10] and are more abundant in terminally differentiated cells, such as brains [11]. In contrast, the expression levels of circRNAs in highly proliferating cells, such as cancer cells, are often low, possibly because of the thinning out by cell proliferation [18].

2. Biogenesis of circRNAs

Many studies have shown that circRNAs are expressed at much lower levels than their associated linear transcripts, and their expression levels do not simply correlate with their linear isoform expression, indicating a potential layer of unknown regulation [19]. Some studies have revealed that circRNA production strongly depends on the presence of canonical splice sites in bracketing exons and spliceosome assembly, indicating that circRNA biogenesis competes with the linear splicing of flanking exons during the canonical splicing machinery [20][21]. However, two reports have shown that depleting the splicing factors or components of U2 snRNPs increases the ratio of circRNAs to linear RNAs [22][23], indicating that the

suppression or slowing of canonical pre-mRNA splicing machinery changes the steady-state production of linear transcripts to circular RNAs.

circRNA formation depends on two mechanisms. The first is base pairing between inverted repeat elements located in both the upstream and downstream introns [24]. In humans, 88% of these inverse-repeat elements are Alu repeats [10][25][26]. Double-stranded RNA (dsRNA)-specific adenosine deaminase (ADAR), which mediates adenosine to inosine editing in endogenous dsRNA, and DexH-Box helicase 9 (DHX9), which catalyzes the ATP-dependent unwinding of double-stranded RNA complexes, suppress the production of circRNAs that depend on base pairing between inverted repeats to prevent the looping of intron sequences [26][27]. In contrast, nuclear factor 90 (NF90) and 110 (NF110), both of which contain a nucleic acid-binding motif (double-stranded RNA-binding motif, dsRBM), promote the biogenesis of circRNAs by stabilizing the base pairing between inversed repeats. The second mechanism involves the dimerization of RNA-binding proteins (RBPs). Quaking (QKI), which belongs to the STAR family of KH domain-containing RBPs, is associated with regions containing recognition elements within a single RNA, resulting in the stimulation of circRNA production [28]. FUS, also known as hnRNPP2, binds to intron regions proximal to the splice junctions involved in circRNA formation and affects the back-splicing reaction [29]. The other RBP of the heterogeneous nuclear ribonucleoprotein family, hnRNPL, binds preferentially to CA-repeat or CA-enriched RNA motifs in introns, resulting in enhanced circulation [30].

After processing in the nucleus, most exon-derived circRNAs are exported into the cytoplasm. RNAi screening assays have revealed that the DEAD box family proteins DDX39A and DDX39B transport circRNAs from the nucleus to the cytoplasm in a size-dependent manner [31].

3. Biological Roles of circRNAs

circRNAs can stably exist in various subcellular fractions, such as the nucleus, cytoplasm, ribosome, cytosol, and exosome, because their loop structures are not affected by the 3′-to-5′ RNA exonuclease RNase R. In general, circRNAs have independent functions from linear transcripts transcribed from the same host genes because of their longer half-lives. Increasing evidence has shown that circRNAs can associate with other regulatory factors, such as microRNAs (miRNAs) and RBPs, and participate in multiple processes, including splicing, transcription, chromatin modification, miRNA sponges, and protein decoys.

3.1. miRNA Sponges

MiRNAs are post-transcriptional regulators that directly bind to mRNAs and inhibit translation or lead to mRNA degradation [32]. In recent years, increasing evidence has suggested that circRNA–miRNA–mRNA regulatory networks are important for exploring the pathogenesis and therapeutic strategies of cancer. One of the most widely investigated functions of circRNAs is to regulate posttranscriptional gene expression by acting as miRNA sponges. These circRNAs localize in the cytoplasm and contain multiple miRNA-binding sequences [10]. CiRS-7 (also termed cerebellar degeneration-related protein 1 antisense RNA (CDR1as)) was the first identified circRNA to harbor more than 70 binding sites for miR-7. MiR-7 is a tumor-suppressive miRNA involved in several pathophysiological pathways in hepatocellular carcinoma, breast cancer, and gastric cancer [33]. CiRS-7 prevents the degradation of miR-7-targeted mRNAs by functioning as a competing endogenous RNA [34].

To date, dozens of cancer-related circRNAs have been found to participate in the occupation of miRNA response elements. Hsa_circRNA_0088036 expression is upregulated in bladder cancer tissues and promotes cancer development by competing with miR-140-3p, resulting in the induction of FOXQ1 [35]. Fang et al. reported that circRNA phenylalanyl-tRNA synthetase subunit alpha (circFARSA) interacts with miR-330 and increases cell proliferation and invasion in bladder cancer tissues [36]. Hsa_circ_0000567 can act as a sponge for miR-421, which increases cell migration and invasion by directly binding to the 3′-UTR of *TMEM100* mRNA in lung adenocarcinoma [37]. Downregulation of circ_0000567 accelerates the development of lung adenocarcinoma via the hsa_circ_0000567/miR-421/TMEM100 axis. CircSYPL1 expression is upregulated in patients with hepatocellular carcinoma; circSYPL1 sponges miR-506-3p to elevate EZH2 expression and induce tumorigenesis in hepatocellular carcinoma cells [38].

3.2. Epigenetic Regulation

Several studies have shown that circRNAs are involved in epigenetic regulation, including histone and chromatin modifications. circIMMP2L mediates the malignancy of esophageal squamous cell carcinoma (ESCC) by promoting the nuclear retention of CtBP1 [39]. In the nucleus, circIMMP2L mediates the interaction between CtBP1 and HDAC1 and induces the deacetylation of histone H3 in the promoter regions of *E-cadherin* and *p21*. CircMRPS35 recruits histone acetyltransferase KAT7 to the *FOXO1* and *FOXO3a* promoter regions, leading to the acetylation of H4K5, which facilitates

the activation of *FOXO1/3a* transcription [40]. FOXO1/3a affects the expression of downstream genes such as *p21*, *Twist1*, and *E-cadherin*, resulting in the suppression of cell proliferation and invasion.

3.3. Transcription and Alternative Splicing

Nuclear circRNAs can regulate gene expression by affecting transcription and alternative splicing, whereas cytoplasmic circRNAs function through interactions with miRNAs or proteins. EIciRNAs, mainly located in the nucleus, interact with U1 snRNP and promote the RNA Pol II-mediated transcription of their parental genes [17]. CircITGA7 downregulates colorectal cancer cell proliferation via facilitating the transcription of its host gene *ITGA7* [41]. Ci-ankrd52, a circular intronic RNA generated from the *ANKRD52* gene, is recruited to its transcription sites to promote RNA Pol II transcription [16].

The effects of circRNAs on pre-mRNA splicing have also been well characterized. CircRPAP2, a circRNA derived from the host gene *RPAP2*, is expressed in breast cancer tissues [42] and inhibits the proliferation and migration of breast cancer by competing with the association between the splicing factors SRSF1 and *PTK2* pre-mRNA to modify the alternative splicing pattern of *PTK2* mRNA. CircURI1 directly associates with hnRNPM to modulate the alternative splicing of a subset of genes involved in cell migration, resulting in the suppression of gastric cancer metastasis [43].

3.4. Protein Decoys

Several circRNAs harbor binding sites for RBPs and act as decoys to suppress protein function. For example, circMbl is derived from the splicing factor *muscleblind* (*mbl*) locus, which harbors multiple binding sites for the MBL protein [20]. CircMbl regulates MBL function by preventing its binding to its target RNAs. CircPABPN1 binds to Hu antigen R (HuR, also known as ELAV-like RNA-binding protein (ELAVL1)) to prevent the association of HuR with *PABPN1* mRNA, resulting in the suppression of the effects of HuR on *PABPN1* translation [44]. Circular antisense non-coding RNA in the *INK4* locus (circANRIL) interacts with pescadillo homolog 1 (PES1) to disrupt pre-rRNA processing mediated by exonuclease in vascular smooth muscle cells [45]. Thus, circANRIL can control ribosome biogenesis to induce nucleolar stress and p53 activation, resulting in the stimulation of apoptosis, which is related to atherosclerosis pathology. Circ-transportin 3 (TNPO3) acts as a protein decoy for insulin-like growth factor 2 binding protein 3 (IGF2BP3) to interfere with the MYC/SNAIL axis, thereby decreasing the proliferation and metastasis of gastric cancer [46]. Chen et al. reported that circ_0000079 associates with Fragile X-Related 1 (FXR1) to interrupt the formation of the FXR1/protein kinase C, iota (PRKCI) complex, which mediates the inhibition of cell invasion and drug resistance in non-small cell lung cancer [47].

3.5. Translation into Peptides/Proteins

Although circRNAs have been categorized as non-coding RNAs, some circRNAs that harbor the open reading frame driven by internal ribosome entry sites are potentially translated into peptides or proteins [48][49]. Circ-ZNF609 exhibits internal ribosome entry site-dependent translation and functions in myoblast proliferation [50]. Zhang et al. reported that the circ-SNF2 histone linker PHD RING helicase (SHPRH) encodes a novel protein, SHPRH-146aa [51]. This truncated protein prevents the full-length SHPRH protein from degradation by the ubiquitin-proteasome and functions as a tumor suppressor in glioblastoma. CircMAPK14-175aa, a peptide of 175 amino acids encoded by the *circMAPK14* gene, reduces the nuclear translocation of MAPK14 by competitively binding to MKK6 and blocking the progression of colorectal cancer [52]. Recent studies have shown that N6-methladenosine (m6A) RNA methylation can drive translation initiation in circRNAs [53]. circRNAs containing m6A are recognized by YTHDF3 and the translation initiation factor eIF4G2. Driven by m6A modification, the m6A reader protein IGF2BP1 promotes circMAP3K4 translation into circMAP3K4-455aa in hepatocellular carcinoma [54]. The expression of circMAP3K4-455aa prevents cisplatin-induced apoptosis and is associated with a worse prognosis in hepatocellular carcinoma patients.

Since most endogenous circRNAs are not associated with ribosomes and the potency of cap-independent translation may be inefficient, further studies are needed to reveal the coding potential of circRNAs.

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