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Mini-review

The emerging functions and roles of circular RNAs in cancer

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ABSTRACT

Circular RNAs (circRNAs) are a class of single-stranded closed RNA molecules that undergo a specific backsplicing from pre-mRNA. With the application of high-throughput sequencing and bioinformatics, circRNAs are found to be widely expressed across species. Some functionally characterized circRNAs have critical roles in gene regulation through various actions, including sponging microRNAs and proteins as well as regulating transcription and splicing. Moreover, most circRNAs are aberrantly expressed in different cancer types, and some of them have been reported to play important roles in the development and progression of cancer. Given the lack of a 5′ cap structure and evidence of their ability to bind with ribosomes, circRNAs were generally considered as noncoding RNA. Notably, recent studies reported that endogenous circRNAs can be translated with a cap-independent manner, which redefines the functional roles of circRNA, further expanding the complexity of eukaryotic transcriptomes. This review aims to re-evaluate the functions and roles of circRNA from the cancer perspective. It discusses the current understanding of circRNA functions, the emerging roles of circRNA in cancer, and the challenges of future studies.

1. Introduction

Circular RNA (circRNA) is a type of recently re-recognized RNA molecular that is renewed attention in the field of RNA. Unlike linear RNAs, circRNAs are single-stranded covalently closed circular transcripts without 5′ caps and 3′ tails [1–4]. CircRNA was first discovered in RNA viruses via electron microscopy in 1976 [5], However, only a handful of circRNAs with little functional potential were serendipitously reported [6–10]. These circRNAs were thought to be 'splicing noise' or by-products of RNA processing with low abundance. CircRNAs have recently become a research hotspot, as recent studies demonstrated their roles in many biological processes [3,4,11–13]. Next-generation RNA sequencing and bioinformatic analysis have discovered that circRNAs are widely expressed across the eukaryotic tree of life [1–3,14–16]. A timeline of significant events in circRNA research is depicted in Fig. 1 [17–19].

Recently, numerous studies have shed light on the biogenesis and function of circRNAs. Circular RNA is commonly processed from precursor mRNA (pre-mRNA) backsplicing of exons [20–22]. Typically, a downstream 5′ splice site (splice donor) of an exon joins an upstream 3′ splice site (splice acceptor) to yield a circular RNA [21]. In addition, circRNA formation is often initiated with the help of reverse complementary sequences, RNA binding proteins or exon skipping [23–25]. Moreover, circRNA expression is cell type and tissue specific [26], suggesting that circRNAs might have biological functions and could be used to classify different tumor types.

Although recent studies have demonstrated that circRNAs can function as a microRNA (miRNA) or RNA binding protein sponge, and regulate splicing or transcription [27], no consensus has been achieved to date in terms of the function of circRNAs, especially the translation of circRNAs. Although some artificial circRNAs with an internal ribosome entry site (IRES) were translated [28–30], no direct biochemical evidence indicates that endogenous circRNAs are capable of protein synthesis. Hence these RNAs were typically thought to be a type of noncoding RNA [20,24,31–34]. Strikingly, in 2017, three groups found that endogenous circRNAs could produce proteins, expanding the complexity, regulation, and function of gene expression in Eukaryota [35–37]. Although many circRNAs are expressed at low levels, emerging evidence has demonstrated that

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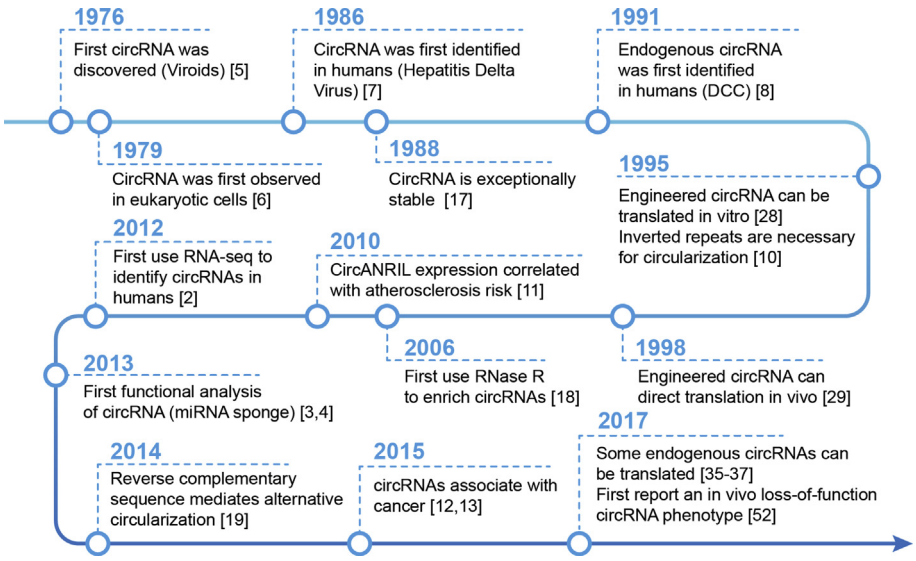

Fig. 1. A timeline of important discoveries in circRNA research.

most circRNAs are aberrantly expressed in different cancer types. Some circRNAs play important roles in multiple aspects of biology and disease, particularly in cancer [23,24].

In this review, we outline the current knowledge on the functions of circRNA, and describe the emerging roles of circRNAs in cancer. We also highlight the potential challenges for future study.

2. Emerging functions of circular RNAs

Considering the low expression of circRNA, these RNAs were overlooked and thought to lack functional significance. However, recently, circRNAs have attracted widespread attention from biological researchers, given that researchers have revealed important functional roles of various circRNAs at multiple levels (Fig. 2).

2.1. CircRNAs serve as miRNA sponges or competing endogenous RNA

The competing endogenous RNA (ceRNA) hypothesis posits that transcripts containing shared miRNA binding sites can affect miRNA activity through sequestration, thereby upregulating miRNA target expression [38]. The ceRNA hypothesis mainly involved three types of RNAs crossing talk to each other, including mRNA, transcribed pseudogenes and long noncoding RNA (lncRNA) [39]. These RNAs communicate through a new “language” mediated by miRNA response elements (MREs) to maintain dynamic balance to regulate cellular homeostasis. Now, the members of ceRNA are further expanded to include circRNA [34].

Most circRNAs are found to be predominantly located in the cytoplasm [22], suggesting the possibility that circRNAs may function as a ceRNA to bind miRNAs. Surprisingly, in 2013, two studies provided the strongest evidence for this notion [3,4]. CiRS-7 (circRNA sponge for miR-7) is also known as antisense to the cerebellar degeneration-related protein 1 transcript (CDR1as), which is highly expressed in human and mouse brains [3]. CiRS-7 harbors greater than 60 selectively conserved miR-7 target sites and is bound but not sliced by miR-7 [4]. Moreover, ciRS-7 and miR-7 exhibit overlapping and specific co-expression in neuronal tissues [3]. Overexpression of ciRS-7 increases the levels of miR-7 targets by suppressing miR-7 activity [4]. In zebrafish, knockdown of miR-7 or expression of ciRS-7 impaired midbrain development [3]. In addition to ciRS-7, the testis-specific circRNA sex-determining region Y (circ-Sry) interacts with miR-138 [4]. These studies represent the first functional analysis of circRNAs, making circRNAs a new star in the RNA field.

Is miRNA sponge achieved by circRNA a general feature? Using a bioinformatic approach, some studies found that no other circRNAs that characterize ciRS-7 were identified as a candidate to act as a strong sponge, and few circRNAs exhibit the properties of miRNA sponges [33,40,41]. However, with the advance of circRNA research, increasing evidence has demonstrated that ciRS-7 and circ-Sry are not an isolated example of circRNAs with ceRNA effects. For example, in a mouse model, circRNA HRCR, a heart-related circRNA named mm9-circ-012559, functions as a miR-223 sponge to regulate cardiac hypertrophy and heart failure induced by isoproterenol and transverse aortic constriction [42]. CircMFACR, another circRNA isolated from heart, regulates the apoptotic pathway in cardiomyocytes by directly sequestering miR-652-3p [43]. In MDA-MB-231 human breast cancer cells, circ-Foxo3, contains 1435 nucleotides (hsa_circRNA_104170) and can bind to eight miRNAs to inhibit the tumor growth and angiogenesis [44]. Several groups reported that circHIPK3 is abundant and derived from exon2 of the *HIPK3* gene. Moreover, circHIPK3 acts as a sponge to multiple miRNAs, including miR-124, miR-558 and miR-30 famliy [45–47]. Other studies have found that circCCDC66 acts as a miRNA sponge to regulate *myc* mRNA through sponging miRNA-33b and miR-93 [48], and that circRNA_100290 may work as a ceRNA to protect CDK6 expression from attack by members of miR-29b family [49]. Another circRNA, circPVT1, binds to and blocks let-7 activity to prevent senescence [50]. CircMTO1 can serve as a sponge of miR-9 [51]. Finally, loss of a mammalian CDR1as in vivo causes miR-7 and miR-671 deregulation and affects brain function [52]. Interstingly, one study found that circRNAs have a decreased single nucleotide polymorphisms (SNP) density at predicted miRNA target sites, indicating that many of these functional sites are under similar selective pressure as miRNA binding sites within 3′ UTRs [53]. Taken together, these findings support the idea that the function of circRNAs as miRNA sponges may be a general phenomenon. These data also provide a pathway to predict the noncoding function of enigmatic circRNA by predicting putative miRNA binding sites.