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REVIEW

The emerging landscape of circular RNA in life processes

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ABSTRACT

Circular RNAs (circRNAs) are a novel class of non-coding RNA that assumes a covalently closed continuous conformation. CircRNAs were previously thought to be the byproducts of splicing errors caused by low abundance and the technological limitations. With the recent development of high-throughput sequencing technology, numerous circRNAs have been discovered in many species. Recent studies have revealed that circRNAs are stable and widely expressed, and often exhibit cell type-specific or tissue-specific expression. Most circRNAs can be generated from exons, introns, or both. Remarkably, emerging evidence indicates that some circRNAs can serve as microRNA (miRNA) sponges, regulate transcription or splicing, and can interact with RNA binding proteins (RBPs). Moreover, circRNAs have been reported to play essential roles in myriad life processes, such as aging, insulin secretion, tissue development, atherosclerotic vascular disease risk, cardiac hypertrophy and cancer. Although circRNAs are ancient molecules, they represent a newly appreciated form of noncoding RNA and as such have great potential implications in clinical and research fields. Here, we review the current understanding of circRNA classification, function and significance in physiological and pathological processes. We believe that future research will increase our understanding of the regulation and function of these novel molecules.

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Introduction

Circular RNA (circRNA) is a novel type of noncoding RNA (ncRNA). Unlike traditionally linear RNA molecules, circRNA is a covalently closed circular molecule without 5'–3' polarities or a polyadenylated tail.[1]

CircRNA was first identified in RNA viruses via electron microscope as early as the 1970s.[2] Unfortunately, only a handful of such circRNAs, including hepatitis delta virus (HDV), *DCC* transcript, *ETS-1*, *Sry* and cytochrome *P450 2C24* (*CYPIIC24*), have been sporadically reported over the past 30 y.[3-9] Hence, circRNAs were typically considered as a byproduct of errant splicing or mRNA process due to low transcript abundance.[6] With the development of high-throughput sequencing technology and bioinformatics, many circRNAs have been discovered and identified,[10-16] leading to a resurgence of interest in these molecules. Recent studies have revealed that circRNAs are stable, conserved and diverse, and often exhibit tissue- or developmental stage-specific expression.[10,11,17-23] To date, the known functions of circRNAs include roles as microRNA (miRNA) sponges[18,24-27] and splicing or transcriptional regulators.[19,28-30] In addition, circRNAs can interact with RNA binding proteins (RBPs).[28,31] Recent studies have implicated circRNAs in the physiological process of aging,[32,33] insulin secretion[34] and tissue development.[35-37] Moreover, circRNAs also have been reported to play crucial roles in the pathological process such as atherosclerotic vascular disease risk,[38] neurological disorders,[1,39] cardiac hypertrophy[27] and cancer.[25,26,40-44] Taken together, these finding indicate that circRNAs might play important roles in fundamental life processes and serve as novel clinical molecular markers, thereby providing new insights into the treatment of diseases.

In this review, we briefly discuss the current understanding of classification and function of circRNAs and highlight their roles in physiology and pathology.

Categories of circRNAs

To provide greater insight into the function of circRNAs, understanding their structure features is critical. Due to their short history of study relative to mRNA, the classification of the vast majority of circRNAs relies on empirical attributes that are based on those of long noncoding RNAs (lncRNAs); this classification system provides a convenient basis on which to classify the former uncharacterized RNA species.

CircRNAs can be generated from any region of the genome, and all result in a great diversity of lengths.[17-20,30,35,45,46] The majority of circRNAs are generated from coding exons: some are derived from the 5' or 3' untranslated regions (5'UTRs or 3'UTRs), whereas others originate from ncRNAs.[18,38] Some circRNAs are derived from introns and are usually excised from pre-mRNA; these species are termed circular intronic RNAs (ciRNAs).[18,19] Interestingly, ciRNAs formation depends

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on a key motif containing a 7-nt GU-rich element close to the 5splice site and an 11-nt C-rich element near the branch point.[19] Finally, circRNAs can be composed of an exon and retained introns, a species termed an exon–intron circRNA, or EIciRNA.[30]

As with lncRNAs,[47,48] we attempt to classify circRNAs based on their genomic proximity to a neighboring gene (Fig. 1). A circRNA can usually be placed into one or more of 5 broad categories: (1) sense or exonic, when arising from one or more exons of the linear transcript on the same strand; (2) intronic, when it is derived wholly from an intron of the linear transcript; (3) antisense, when it overlaps one or more exons of the linear transcript on the opposite strand; (4) bidirectional or intragenic, when it is transcribed from same gene locus of the linear transcript but in close genomic proximity and not classified as 'sense' and 'intronic'; and (5) intergenic, when it is located in the genomic interval between 2 genes.

Biological functions of circRNAs

Although the abundance of circRNAs is now recognized, the potential function of these molecules remains the issue of debate. Recent studies have revealed 3 possible biological functions of circRNAs. Specifically, they can function as miRNA sponges, regulate transcription or splicing, and interact with RBPs (Fig. 2).[1,49-52]

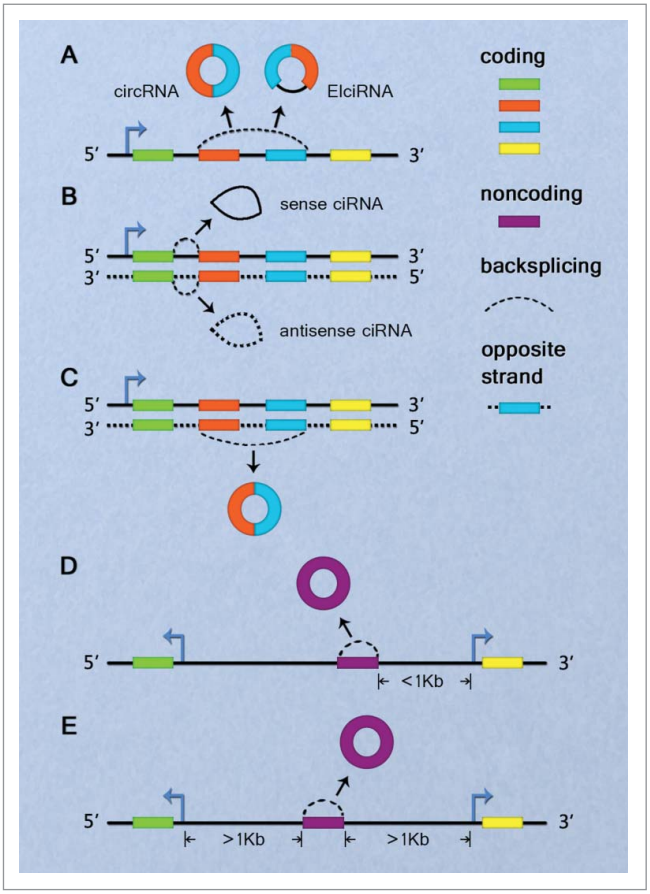

Figure 1. Schematic presentation of circRNA classification. (A) Sense or exonic, when overlapping one or more exons of the linear transcript on the same strand. (B) Intronic, when arising from an intron of the linear transcript in either sense or antisense orientation. (C) Antisense, when overlapping one or more exons of the linear transcript, as they transcribe from the opposite strand. (D) Bidirectional or intragenic, when transcribing from same gene locus of the linear transcript, but in close genomic proximity within 1 kb and not classified into 'sense' and 'intronic'. (E) Intergenic, when it locates outside at least 1kb away from known gene locus.

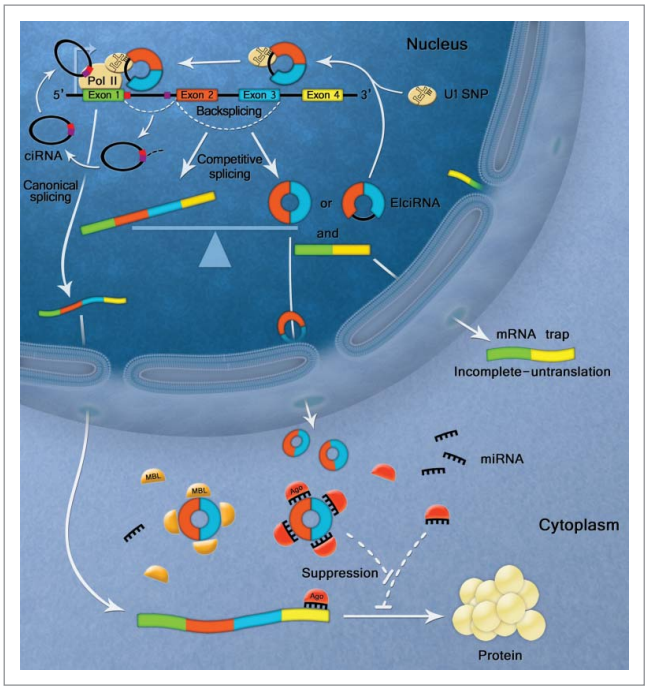

Figure 2. Biological functions of circular RNAs. CircRNAs contain miRNA binding sites to act as competitive endogenous RNA. CircRNAs sequester miRNAs from binding mRNA targets. EIciRNAs can enhance gene transcription via interacting with U1 snRNP and RNA Polymerase II in the promoter region of the host gene. GU-rich sequences near the 5′ splice site (red box) and C-rich sequences near branch point (purple box) are minimally sufficient for ciRNA formation. The stable ciRNA binds to elongating RNA Pol II and promotes transcription. CircRNA biogenesis competes with linear splicing. Circularization and splicing compete against each other to keep the transcripts dynamic balance. CircRNA formation act as 'mRNA trap' to make linear transcripts untranslated by sequestering the translation start site or break the integrity of mature linear RNA. CircRNAs can also function as RNA binding protein (RBP) sponge to interact with RBPs, such as MBL, p21 and CDK2.

Considering the stability of their circular structure and their conserved sequences, circRNAs are ideal to act as miRNA sponges or competitive endogenous RNAs (ceRNAs). Seven circRNAs - ciRS-7/CDR1as (for circular RNA sponge for miR-7 or *CDR1* antisense),[18,24] *Sry* circRNA (circ-Sry),[24] circ-ITCH,[25,43] circ-Foxo3,[26] circRNA *HRCR*,[27] circHIPK3[53] and hsa_circ_001569[54] - have been verified to function as miRNA sponges. The ciRS-7/CDR1as molecule contains more than 70 miR-7 binding sites and can adsorb miR-7 to reduce its miRNA activity.[24] circ-Sry is highly expressed in adult mouse testis;[7] it harbors 16 miR-138 binding sites and interacts with miR-138.[24] Although these 2 examples are striking, the 2 circRNAs have a larger number of putative miRNA binding site. It is currently debated whether the function of circRNA as an miRNA sponge is a general (but not exclusive) feature.[49] Two studies indicated that most circRNAs do not function as miRNA sponges as a large majority of circRNAs does not possess more miRNA binding sites than do co-linear mRNAs.[20,29] However, with the advance of circRNA research, increasing evidence indicate that circRNA can act as miRNA sponge, which may not depend on the numbers of miRNA binding site. For example, circ-ITCH was also found to function as a sponge of miR-7, miR-17 and miR-124 via luciferase reporter assays.[25] Yang

and coworkers recently discovered that *circ-Foxo3* could serve as an effective miRNA sponge through its interaction with miR-22, miR-136*, miR-138, miR-149*, miR-433, miR-762, miR-3614–5p and miR-3622b–5p.[26] Moreover, 3 recent studies just found that circRNA *HRCR*,[27] circHIPK3[53] and hsa_circ_001569[54] could act as miRNA sponge, such as miR-223, miR-124 and miR-145. These findings support the idea that circRNA acting as miRNA sponges is a widespread phenomenon in many eukaryotes.

Because of the correlation between circRNAs and their parent gene, the formed are thought to positively regulate parent gene expression in *cis*- or *trans*-acting manner. ciRNA was found to localize to the nucleus and to interact with the Pol II machinery to activate its parent gene transcription.[19] Similarly, EIciRNAs was shown to localize predominantly to the nucleus and to interact with U1 snRNP and Pol II through complementary sequence pairing between EIciRNA and U1 snRNA (snRNPs), thereby enhancing the transcription of its parental gene.[30] Later, circ-ITCH was reported to act as a sponge of miR-7, miR-17 and miR-138 to increase the level of ITCH.[25] Notably, The pocessing of circRNAs also affects splicing. There is a negative correlation between circRNA formation and alternative splicing, potentially leading to altered gene expression. circMbl formation competes with *mbl* pre-mRNA splicing. circMbl and circMbl flanking introns harbor conserved MBL protein binding sites that bind strongly to MBL. The alteration of MBL level significantly affects circMbl formation, an effect dependent on MBL binding sites.[28] Moreover, backsplicing may produce circRNA and a corresponding linear RNA.[28] The circRNA may contain a translation start site, leaving the corresponding linear RNA untranslated.[17,29,55] Alternatively, circRNA formation may disrupt the integrity of mature linear RNA, also leaving it untranslated.[56] This phenomenon is known as an mRNA trap.[55]

Like lncRNA, circRNAs can interact with RBPs or function as RBP sponges.[28,31,57] As described above, circMbl contains conserved MBL protein binding sites. MBL can interact with circMbl to balance the efficiency between circMbl and *mbl* mRNA production.[28] Moreover, Du and others found that circ-Foxo3 could interact with both CDK2 and p21 forming a ternary complex, blocking cell cycle progression,[31] and that circ-Foxo3 could promote cardiac senescence by modulating multiple factors associated with stress and senescence responses, such as ID-1, E2F1, FAK, and HIF1α.[57]

CircRNAs in the life processes

CircRNAs are stable, conserved noncoding RNAs with cell-, tissue-, and developmental stage-specific patterns of expression. Because circRNAs have the above functions, they are the subject of much recent attention. Recent studies have suggested that circRNAs play important roles in biological processes and have the potential to become clinical molecular biomarkers (Table 1).

Table 1. circRNAs in the life processes.

Circular RNA	Biological process	References
CDR1as/ciRS-7	Regulate the development of midbrain via acting as miR-7 sponge in zebrafish embryos	18
	Promote insulin biosynthesis and secretion through CDR1as/miR-7 pathway in islet cells	34
circRNA *cZNF292*	Control proliferation and angiogenic sprouting of endothelial cells	58
hsa_circ_0023404/ circRNA-*CER*	Participate in the process of chondrocyte extracellular matrix degradation	64
cANRIL	Regulate *INK4/ARF* transcription and atherosclerotic vascular disease risk	38
mm9-circ-012559/ circRNA *HRCR*	Protect the heart from pathological hypertrophy and heart failure via targeting miR-223 in mice	27
circ-ITCH	Inhibit cell proliferation and tumor growth via acting as a sponge of miR-7, miR-17 and miR-124 in esophageal squamous cell carcinoma	25
	Inhibit cell proliferation via interacting with miR-7, miR-20a and miR-214 in colorectal cancer	43
circ-Foxo3	Suppress tumor growth, cancer cell proliferation and survival in breast cancer (MDA-MB-231 cell)	26
	Block cell cycle progression by forming a ternary complex with CDK2 and p21	31
	Promote cardiac senescence by modulating ID-1, E2F1, FAK, and HIF1α in mice	57
circHIPK3	Inhibit human cell growth by sponging multiple miRNAs	53
hsa_circ_001569	Promote the proliferation and invasion of colorectal cancer cells	54
F-circM9	Contribute to leukemia progression and confer resistance to treatment in leukemic cells	70

CircRNAs in the physiological processes

Recent studies have indicated that circRNAs may be involved in essential physiological processes. For example, CDR1as expression was up-regulated in islet cells by the PMA and long-term forskolin stimulation but not high glucose levels. Strikingly, CDR1as overexpression significantly promotes insulin biosynthesis and secretion through the CDR1as/miR-7 pathway, which provides a potential target for improving β cell function in diabetic patients.[34] Boeckel et al. found that circular RNAs are expressed in endothelial cells and are regulated by hypoxia. The circular RNA *cZNF292* controls the proliferation and angiogenic sprouting of endothelial cells. These findings indicate that endothelial circRNAs are regulated by hypoxia and have a biological function.[58] Moreover, a large number of circRNAs were shown to be dysregulated in the absence of CD28 in CD8(+) T cells during aging using a circRNA microarray approach. The identification of a circRNA-miRNA-gene network suggested that circRNA100783 might regulate phosphoprotein-related signal transduction in the context of CD28-dependent CD8(+) T cell aging.[33]

Interestingly, circRNAs play crucial roles in physiological processes in non-human mammals. CDR1as harbors 74 miR-7 seed matches that are often highly conserved. Moreover, CDR1as is expressed at higher levels in nervous tissue.[18,59] The overexpression of CDR1as in zebrafish embryos substantially reduces the size of the midbrain, phenocopying the morphological defects in the midbrain the accompany miR-7 loss-of-function.[18] Some studies have shown that circRNAs are highly abundant in the mammalian brain[35,37,60] and are especially

enriched in synaptoneurosomes.[36] Many circRNAs alter their abundance during synaptogenesis and neuronal differentiation.[35,36] Moreover, Westholm et al. reported that circRNA levels increased substantially in the central nervous system during aging compared with the levels of the corresponding co-linear isoforms and might serve as aging biomarkers in *Drosophila*.[32] These data indicated that circRNAs could be involved in neuronal differentiation or development and might act to regulate synaptic function. Remarkably, Abdelmohsen and others have identified circRNAs that are abundantly expressed in the skeletal muscle tissues of Rhesus monkey. Among these, they found that subsets of circRNAs exhibited age-dependent expression patterns.[61] Taken together, these findings suggest roles for circRNAs in the physiological processes.

CircRNAs in the pathological processes

A growing body of research has demonstrated that circRNAs play crucial roles in the initiation and development of diseases and might function as novel biomarkers for disease diagnosis and therapy.

CircRNAs and neurological diseases

For example, Satoh et al. reported that the stable overexpression of prion protein (PrPC) in HEK293 cells induced the expression of CDR1as but not *CDR1*.[62] Hence, PrPC might be involved in the regulation of CDR1as expression. It would be worth elucidating the function of CDR1as in prion diseases. Besides, Kuliw detected that the level of ciRS-7 is significantly reduced in sporadic Alzheimer disease (AD) compared to its expression in age-matched control hippocampal CA1.[39] Intriguingly, previous studies found that miR-7 can act as a direct regulator of ubiquitin protein ligase A (UBE2A), which is essential for the clearance of amyloid peptides in AD,[39] and miR-7 can down-regulate α-synuclein expression, which is implicated in Parkinson disease (PD).[63] Considering ciRS-7 can function as miR-7 sponge, these findings suggests that *ciRS-7* may play a role in AD and PD.

CircRNAs and cardiovascular diseases

cANRIL (circular antisense non-coding RNA in the *INK4* locus, *cANRIL*) is an antisense transcript synthesized from the *INK4/ARF* locus. Burd and others have found that *cANRIL* isoform expression is associated with *INK4/ARF* transcription and atherosclerotic vascular disease (ASVD) risk. Interestingly, 9p21 polymorphisms within the ASVD risk interval may regulate *ANRIL* splicing and *cANRIL* production, as determined using next-generation DNA sequencing and splice prediction algorithms.[38] It would be interesting to unveil the function of *cANRIL* in ASVD.

Wang et al. found that circRNA *HRCR* inhibit the development of cardiac hypertrophy and heart failure induced in the mice by isoproterenol and transverse aortic construction via miR-223.[27] Moreover, ectopic expressed circ-Foxo3 could bind to senescence-related proteins ID1 and E2F1, and stress related proteins HIF1α and FAK in cytoplasm, promote cardiac senescence.[57] These results provide new insights for understanding the pathogenesis of heart diseases.

CircRNAs and degenerative diseases

Both circMbl and its flanking intron sequences can be bound by MBL, and the modulation of MBL level strongly affects circMbl formation. circRNA biogenesis competes with canonical *mbl* pre-mRNA splicing.[28] MBL has been shown to regulate the *mbl* pre-mRNA splicing efficiency of circMbl and *mbl* mRNA. Moreover, circMbl can serve as a sponge for MBL, thereby regulating the production of MBL protein. However, MBL functional deficiency is known to be involved in a severe degenerative disease called myotonic dystrophy.[1] We therefore speculate that circMbl could be associated with the initiation and development of myotonic dystrophy. In addition, Liu and others demonstrated that some circRNAs were differently expressed in osteoarthritis, and that circRNA-*CER* could regulate MMP13 expression by competitively binding miR-136 in human cartilage degradation. [64]

CircRNAs are dysregulated in cancer

In cancer biology, it is very important to identify gene expression differences between tumor and normal samples, as knowledge of circRNA expression signatures in tumor and normal samples is necessary. Moreover, recent research has demonstrated that circRNAs are globally down-regulated in colorectal cancer (CRC) tissues compared to matched normal tissues and are even more reduced in CRC cell lines. Interestingly, a negative correlation between global circular RNA abundance and proliferation has been reported.[41] In addition, recent studies also found that circRNA expression patterns were dysregulated in pancreatic cancer,[40] basal cell carcinoma,[65] cutaneous squamous cell carcinoma,[66] laryngeal squamous cell carcinoma,[67] hepatocellular carcinoma[68] and glioma[69] via microarray or sequencing technology. These findings indicate that dysregulated circRNAs may be involved in the development of some cancer. However, whether circRNAs are dysregulated in other tumor remains to be clarified.

Remarkably, Guarnerio and others[70] found a novel type of circRNA derived from cancer-associated chromosomal translocations: aberrant fusion-circRNAs (f-circRNA). F-circRNAs are oncogenic and contribute to cellular transformation. Especially, F-circM9 contributes to leukemia progression and confers resistance to treatment in leukemic cells.

CircRNA–miRNA axes are involved in cancers

CircRNAs, which have emerged as new transcriptome regulators, constitute an exciting new field of biological inquiry. Recent studies have demonstrated that circRNAs are associated with disease-related miRNAs. It is clear that miRNAs are involved in nearly all aspects of cellular functions and play important roles in disease initiation and progression.[71,72] Because many circRNAs contain several conserved binding sites for miRNAs,[32,73] circRNAs could interact with miRNAs to control their biological function. This crosstalk between circRNAs and miRNAs is the key to understanding the role of circRNAs in carcinogenesis and other diseases.[74,75]

For example, CDR1as has been confirmed to bind specifically to miR-7 and to inhibit its biological function.[24] Furthermore, miR-7 has been shown to play oncogenic or tumor-suppressive roles in cancers.[76-79] Hence, the CDR1as/miR-7 axis may perform an essential regulatory role in cancer-associated pathways. In parallel, circ-Sry controls the biological functions of miR-138 by binding to its 16 binding sites.[24] miR-138 has also been shown to play important roles in cancer.[80] It would therefore be interesting to explore the functions of the circ-Sry/miR-138 axis in cancer.

Remarkably, Li et al. found that circ-ITCH expression is commonly downregulated in esophageal squamous cell carcinoma compared to paired adjacent tissues. circ-ITCH can increase the level of ITCH by acting as a sponge for miR-7, miR-17 and miR-124, which promote the ubiquitination and degradation of phosphorylated Dvl2 to inhibit the expression of the oncogene *c-myc*, thereby suppressing the canonical Wnt signaling pathway.[25] Subsequent parallel study has shown that circ-ITCH expression is also usually down-regulated in CRC, and that circ-ITCH can also increase the level of ITCH by interacting with miR-7, miR-20a and miR-214, thereby suppressing the Wnt/β-catenin pathway.[43] Moreover, hsa_circ_001569 is upregulated in CRC, and promotes the proliferation and invasion of CRC cells by regulating miR-145 and its targets.[54] Specifically, 2 recent studies respectively have demonstrated that the overexpression of circ-Foxo3 in MDA-MB-231 cells suppresses tumor growth in vivo as well as cancer cell proliferation and survival *in vitro*,[26] and that silencing of circHIPK3 RNA inhibits human Huh7, HCT-116 and HeLa cell proliferation by sponging with miR-124.[53]

CircRNAs as a source of diagnostic markers

CircRNAs are more stable than linear RNAs due to their higher nuclease stability and exhibit long half lives in cells.[17,19,81] These features are an enormous clinical advantage for use as diagnostic and therapeutic biomarkers for cancers. For instance, hsa_circ_002059 was found to be commonly downregulated in gastric cancer, which was associated with TNM stage and distal metastasis. Hence, hsa_circ_002059 was regarded as a potential novel biomarker for the diagnosis of gastric cancer.[42] Similarly, hsa_circ_0001649 expression was significantly down-regulated in hepatocellular carcinoma (HCC), which was correlated with tumor size and the occurrence of tumor embolus. Thus, hsa_circ_0001649 is a novel putative biomarker for HCC.[44]

Intriguingly, circular RNA has been shown to be enriched and stable in exosomes (small membrane vesicles containing endocytic origins secreted by cells). Moreover, the abundance of tumor-derived exosomal circRNAs in the serum of xenografted mice was correlated with tumor mass, which may serve as a promising biomarker for cancer detection.[46] Remarkably, Memczak and colleagues observed that circRNAs are reproducibly and easily detected in clinical standard blood samples. Hundreds of circRNAs are expressed at much higher levels than their corresponding linear mRNAs in human blood, suggesting that they may represent a new class of biomarkers for human disease.[82] Likewise, Bahn and others predicted 422 putative circRNAs in human cell-free saliva using high-throughput RNA sequencing. Some of these predicted circRNAs were validated by RT-PCR using divergent primers. All PCR products were purified and subjected to Sanger sequencing.[83] Considering the urgent clinical need for non-invasive biomarker detection for many disease states, circRNA biomarkers in human blood and saliva or other bodily fluids appear very promising.

Conclusion and perspective

In the past, circRNAs were considered a byproduct of aberrant splicing events or intermediates that had escaped from intron lariat debranching.[6,84,85] Thus, they were thought to be unlikely to play crucial roles in biological processes. Nevertheless, with advancements in high-throughput sequencing technologies and bioinformatics, circRNAs were found to be broadly expressed and to perform co- or post-transcriptional regulation in the cells and tissues of various species. Moreover, multiple circular RNAs have been identified from a single precursor RNA in a phenomenon referred to as alternative circularization.[21] These findings greatly expanded our knowledge of the complexity of gene regulation and have moved circRNA to the forefront of biological research. Along with in-depth studies of circRNAs, several circRNA databases have been constructed, such as circBase (http://www.circbase.org/),[86] circNet (http://circnet.mbc.nctu.edu.tw/),[87] Circ2Traits (http://gyanxet-β.com/circdb/)[74] and CircInteractome (http://circinteractome.nia.nih.gov).[88] These databases provided excellent platforms to facilitate further functional research on circRNAs.

To date, studies have revealed that circRNAs are evolutionarily conserved and are expressed in a cell-, tissue- and developmental stage-specific manner. Although the functions of circRNAs are largely unknown, accumulating evidence has shown that circRNAs function in multiple biological processes, such as miRNA binding, protein binding and regulation of transcription or splicing.[1,52] Remarkably, endogenous circRNAs have not been found to associate with ribosomes for translation, suggesting that they have a tendency to serve as a new class of ncRNAs. Nevertheless, exogenous circRNAs engineered to contain an internal ribosome entry site (IRES) or via a rolling circle amplification mechanism can be translated *in vivo* or *in vitro*,[89,90] so we cannot exclude the possibility that some circRNAs are translatable. As studies of circRNAs increase in number, it is likely that additional functions will be revealed.

Strikingly, recent studies have also reported that circRNAs play essential roles in the physiological processes of aging, insulin secretion and tissue development. Moreover, circRNAs are reported to be involved in the pathological processes, especially cancer. Hence, these findings indicate that circRNAs might play important roles in biological processes, serve as novel clinical molecular biomarkers and provide insight into the treatment of diseases. However, current studies of the relationship between circRNAs and disease physiology and pathology are limited. In the near future, if properly modified and delivered, circRNAs have the potential roles to act as molecular tools or therapies to regulate cellular homeostasis by interacting with miRNAs and other RNAs or RBPs.

The study of circRNAs has gradually become one of the hottest topics in the field of genetics. However, the field of circular RNA presents a wealth of unanswered questions. Currently, several bioinformatic algorithms such as find-circ,[18]

MapSplice,[91] CIRCexplorer,[21] circRNAfinder[32] and CIRI[92] are available to predict circRNAs. However, the consistency of these computational tools remains relatively low, and no systematic approach is available for identifying circRNAs in the human transcriptome. There remains a need for a robust algorithm to achieve more reliable predictions with a better balance between precision and sensitivity.[51,93] Given the huge number of circRNAs and the empirical classification of circRNAs based on lncRNA categories, it is important to develop a standard nomenclature or a comprehensive classification system to enable future circRNAs research. Moreover, current studies of circRNAs have mainly focused on circRNA formation, whereas little is known about the degradation of most circRNAs. A possible mechanism for circRNA clearance is to eliminate them via releasing vesicles such as microvesicles and exosomes.[94] The expression profiles of circRNAs maybe depend on a balance between biogenesis and degradation. Moreover, given that cellular localization is often associated with physiological function and mechanism, it is a topic worth exploring.

Taken together, although circRNAs are currently in the spotlight, the field is still in its infancy. Further intensive studies are needed to explore the molecular and biological functions of circRNAs. The world of the transcriptome may be more complicated than previously thought. circRNA, as the new star of noncoding RNA, would be widely involved in the regulation of physiological and pathophysiological processes, serve as stable clinical biomarkers of disease, and also provide new potential therapeutic targets.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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