Review

Circular RNAs in Brain Disorders

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ABSTRACT

Circular RNAs, a class of covalently closed transcripts, are generated from thousands of protein-coding genes or noncoding regions of the genome via non-canonical splicing, and serve as important controllers in a variety of biological events in eukaryotes. Emerging studies have shown that circular RNAs are enriched in animal brains, and involved in brain disorders. In this review, we will discuss recent progress on circular RNA biogenesis, nuclear export, stability control, molecular functions, and regulatory roles in brain functions.

KEYWORDS: circular RNA; brain disorder; clinical biomarker

INTRODUCTION OF CIRCULAR RNA BIOLOGY: BIOGENESIS, NUCLEAR EXPORT, DEGRADATION, AND MOLECULAR FUNCTIONS OF CIRCULAR RNAS

Biogenesis

Although a subset of circular RNAs are generated from noncoding regions, most of them are outputs of many protein-coding genes via backsplicing. In contrast to canonical splicing that joins the exons in a linear order (5' to 3' end), backsplicing joins the 3' end of exon to the 5' end of an upstream exon, and are typically controlled by various factors. (i) *Flanking intronic repeats*: in many cases, base pairing between the flanking intronic repeats of circularizing exons brings a splicing donor and an upstream splicing acceptor in close proximity and facilitates circular RNA production (Figure 1A) [1–3]. There are many highly expressed circular RNAs are flanked by a pair of complementary repeats. Interestingly, due to the diverse landscape of complementary repeats, the conserved protein-coding genes produce different circular RNAs in different species. (ii) *Protein factors*: a subset of circular RNAs that are not flanked by complementary repeats are circularized by several RNA binding proteins. A well-known RNA binding factor—Quaking acts analogously as flanking repeats and facilitates circularization of hundreds of circular RNAs. During human epithelial-mesenchymal transition, Quaking directly binds to the upstream and downstream flanking intron of circularizing exons, resulting in close proximity of splicing sites (Figure

1B) [4–7]. (iii) ***Exon skipping events***: Using RNA-seq, Kelly *et al.* found that circularization of exons is correlated with exon skipping events globally in human umbilical vein endothelial cells, and Barrett *et al.* identified that mrps16 can generate a circular RNA via exon skipping in *S. pombe* (Figure 1C) [8,9]. (iv) ***Intron retention***: although most introns are moved, a class of RNA polymerase II binding circular RNAs were reported to be circularized with introns "retained" between exons, and thus termed as exon-intron circular RNAs (EIciRNAs; Figure 1D) [10]. (v) ***Splicing machinery***: Recent study found that circular RNAs become the preferred gene products when core spliceosomal components were depleted from cells or canonical mRNA splicing events were inhibited by Pladienolide B (Figure 1E), suggesting that the biogenesis of circular RNAs and their linear counterparts remain in a dynamic balance [11].
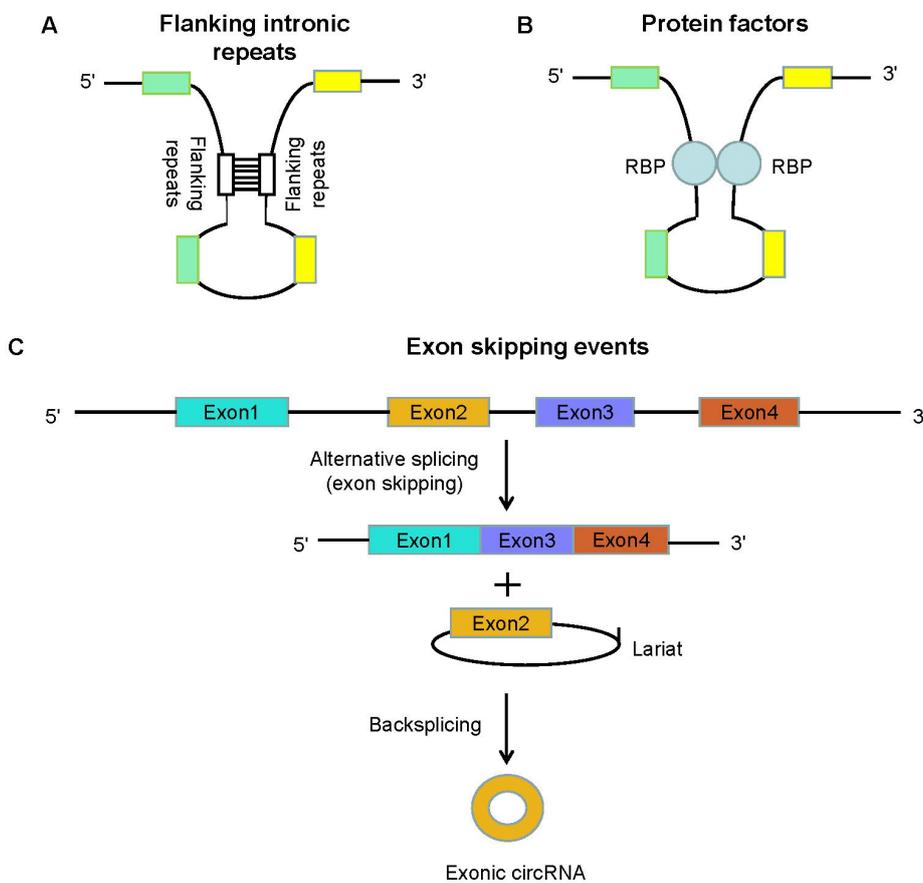

Figure 1. The biogenesis of circular RNAs. (**A**) Many circular RNAs trend to be flanked by intronic repeats. Base pairing between the flanking intronic repeats of circularizing exons facilitates backsplicing events that a splicing donor joins an upstream splicing acceptor. (**B**) In some cases, RNA-binding proteins (RBPs) act analogously as flanking repeats via direct interaction with flanking intron. (**C**) Circular RNA can also be generated by exon skipping events that result in a linear RNA and an exon-containing intron lariat, which is re-spliced to generate a mature exonic circular RNA. (**D**) Exon-intron circular RNAs are circularized with introns "retained" between exons. (**E**) The dynamic balance between linear and circular transcripts are controlled by spliceosome. Circular RNAs become the major gene products when core spliceosomal components were inhibited.
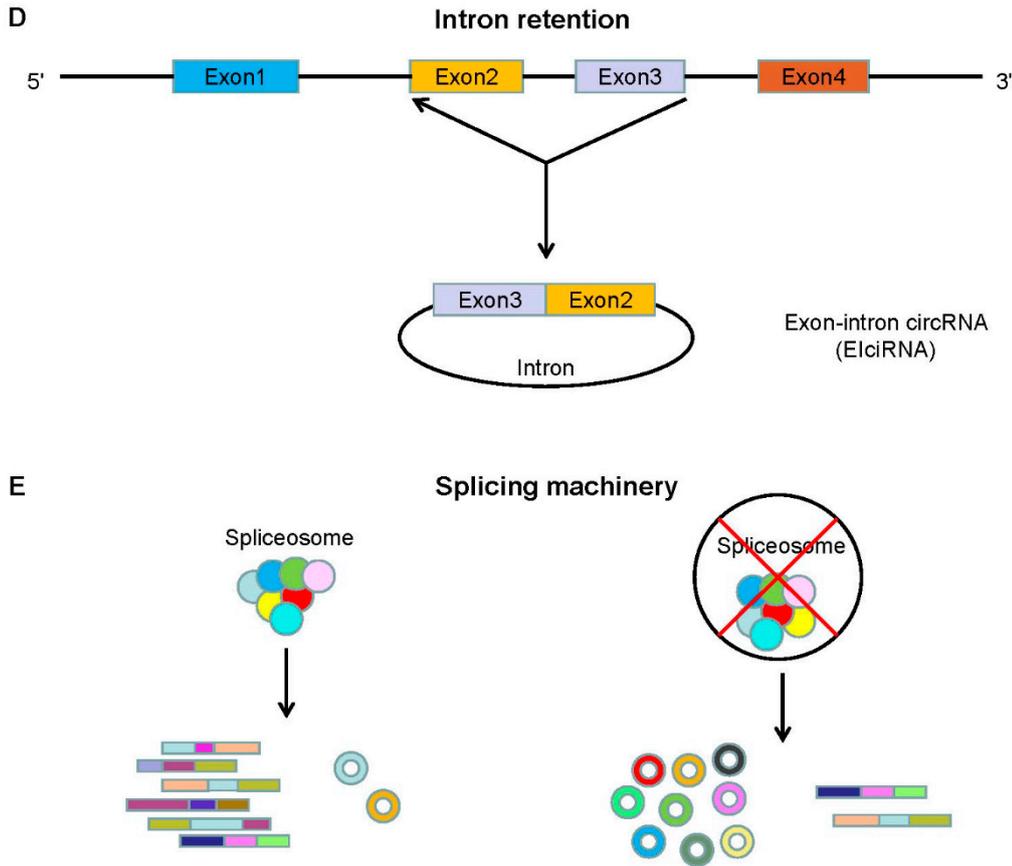
Figure 1. *Cont.*

Nuclear Export

Nuclear export of cytoplasmic circular RNAs is important to their proper functions. Although intronic or intron-containing circular RNAs are retained in the nucleus [10,12], most circular RNAs are efficiently exported to the cytoplasm [13,14]. Due to lack of canonical export signals, circular RNAs were thought to reach the cytoplasm upon nuclear envelope breakdown during cell division. However, recent studies proved that nuclear export of circular RNAs is an active process and regulated by conserved factors-UAP56 (DDX39A) and URH49 (DDX39B) in a size-dependent manner [15–17]. Long circular RNAs (>1298 nt) are exported by UAP56, while short circular RNAs (<356 nt) are exported by URH49 (Figure 2). Surprisingly, a four amino-acid region (KSLN in UAP56; RSFS in URH49) can determine circular RNA size preference.
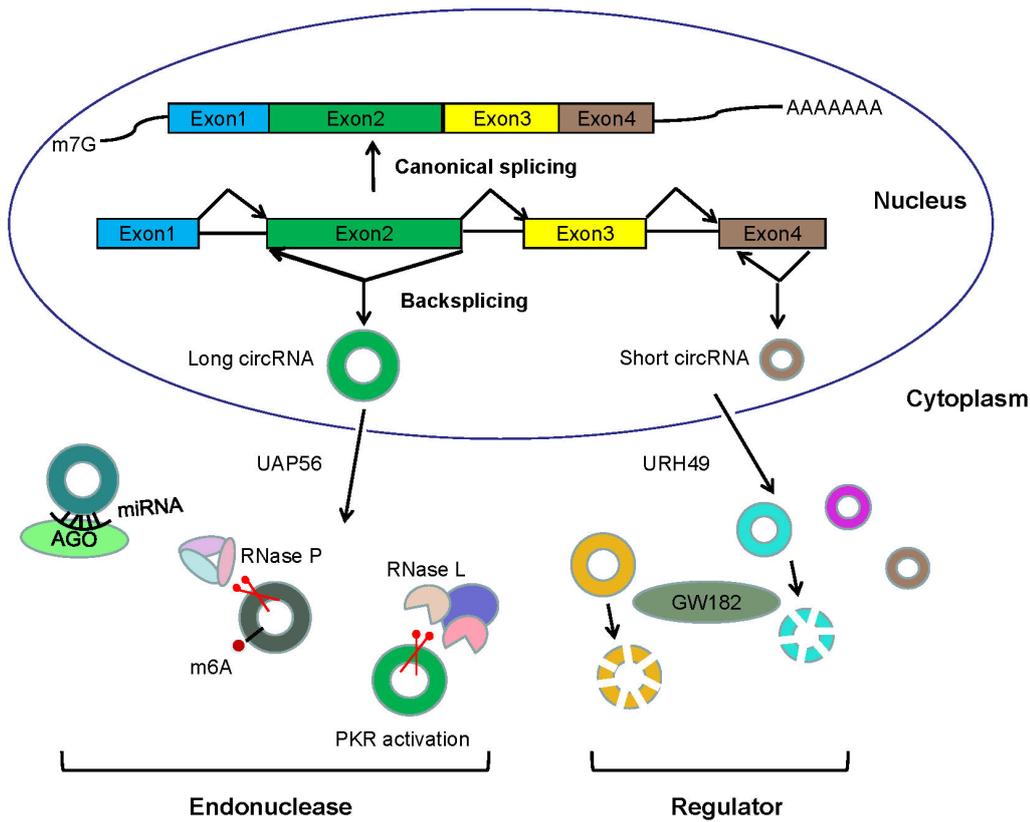
Figure 2. The nuclear export and degradation of circular RNAs. Circular RNAs are exported to cytoplasm in a size-dependent manner. UAP56 controls long circular RNA export, whereas URH49 controls short circular RNA export. Circular RNAs degradation is triggered by three endonuclease (AGO, RNase P, and RNase L), and promoted by an evolutionarily conserved factor-GW182.

Degradation

Different from most species of linear RNAs, circular RNAs are naturally resistant to exonuclease, and have long half-lives for their lack of 3' and 5' end. Depletion of several canonical RNA degradation factors had little effect on circular RNA levels, suggesting that circular RNA degradation seems to employ a regulatory pathway that is distinct from linear RNAs'. (i) *AGO*: An early study demonstrated that near perfect microRNA binding sites can trigger cleavage of some circular RNAs in an Ago-slicer-dependent pathway (Figure 2) [18]. The most well-known example is ciRS-7 (circular RNA sponge for miRNA-7) which has complementary target sites for miRNA-671. The interaction with miRNA-671 directs cleavage of ciRS-7 by Ago2 in human cells. (ii) *GW182*: Using RNAi screening strategy, our group identified an evolutionarily conserved factor (GW182 in *Drosophila*; TNRC6A, TNRC6B, and TNRC6C in human) controls circular RNA stability in a P-body or AGO independent manner recently (Figure 2). Surprisingly, the expression of parental linear RNAs were not affected upon GW182 depletion [19]. Although GW182's role in circular RNA stability control is yet to be identified, we hypothesize that GW182 might act as ae a molecular platform to recruit many decay factors, or GW182 might affect the subcellular localization of circular RNAs. (iii) *RNase P*

and RNase L: m^{6}A-modified circular RNAs have been shown to associates with YTHDF2 in an HRSP12-dependent manner and be cleaved by an endonuclease—RNase P selectively (Figure 2) [20]. Circular RNA degradation is also associated with innate immunity. RNase L, a widely expressed cytoplasmic endonuclease, can mediate circular RNA degradation genome-widely upon viral infection and PKR activation (Figure 2) [21].

Molecular Functions

Circular RNAs have diverse molecular functions in eukaryotic cells. (i) *MircoRNA sponges*: many studies have proved that plenty of exonic circular RNAs have multiple microRNA binding sites, and thereby can sequester microRNAs in the cytoplasm to control gene expression [22–28]. For example, circHIPK3 acts as a sponge to modulate cell growth and division by decreasing activities of multiple microRNAs [24]. "Circular RNA-microRNA-mRNA" axis serves as a new way of post-transcriptional regulation. (ii) *Transcriptional regulation*: RNA polymerase II associated exon-intron circular RNAs were found to control their parental mRNA production in the nucleus via RNA-RNA interaction with U1 snRNP [10]. Blocking the RNA-RNA interaction impairs the interactions of EIciRNAs with parental gene promoter and RNA polymerase II, thereby decreasing transcription activities of their parental mRNAs. (iii) *Splicing regulation*: A role of circular RNAs in splicing events has also been proved by the observation that circSEP3 is able to control SEP3 mRNA splicing and induce transcriptional pausing by forming a strong DNA-RNA hybrid with its cognate DNA locus in *Arabidopsis* [29]. (iv) *Translation templates*: Due to lack of both 5' caps and 3' ploy(A) tails, most circular RNA were first thought to be untranslatable. However, a small subset of natural circular RNAs were found as translation templates that can be used to produce proteins [30–32]. For example, a conserved and highly expressed circular RNA—circZNF609 contains an open reading frame and encodes a protein in a cap-independent manner, but the functions of these circular RNA-encoded proteins are yet to be defined [30]. (v) *Protein subcellular localization*: two mitochondrial genome encoded circular RNAs (mecciRNAs) were reported to be involved in mitochondrial protein import via a polynucleotide phosphorylase (PNPASE), indicating that at least a subset of circular RNAs might affect protein subcellular localization [33]. However, the transportation and production of these mecciRNAs still remain unknown.

CIRCULAR RNA IN BRAIN DISORDERS

Most circular RNAs have been reported to be weekly expressed [13,14,34,35]; however, some circular RNAs are more abundant than their parental linear counterparts [36–39]. In *Drosophila* DL1 cells, circlaccase2 expression is ten times higher than linear laccase2 mRNA, suggesting at least a subset of circular transcripts are major products of certain genes

[3,11]. Surprisingly, comprehensive sequencing data demonstrated that there are thousands of circular transcripts accumulating in animal brains during aging and neuronal differentiation [30,35–37,40–44]. Following induction of neuronal activity and plasticity, the expression pattern of circular RNAs changes, while their parental linear counterparts are little affected. It will be interesting to explore the mechanism of such circular-linear transcripts balance regulation. Furthermore, some brain-enriched circular RNAs are evolutionarily conserved in expression and sequence from *Drosophila* to human [37,43]. Finally, there are much more circular RNAs in human brains than that in mouse brains. The probable reason is that these circular transcripts are not equally distributed in animal brains, but highly enriched in the synapses, and the synaptic density in human cerebral cortex is much higher than that in mouse [36,37]. Together, these data indicate that brain-enriched circular RNAs may have roles in brain functions.

Circular RNA in Alzheimer's Disease

Emerging studies have shown that circular RNAs are correlated with Alzheimer's disease (AD), which is a form of dementia and a neurodegenerative disease that progresses slowly over time among old people. ciRS-7 has been shown to be an endogenous mircoRNA sponge that sequester miRNA-7 via base pairing, thereby suppressing its functions and modulating its targets' translation [22]. ciRS-7 is dramatically downregulated in Alzheimer's disease affected brain cells compared to age-matched control hippocampal CA1, resulting in significantly accumulated miRNA-7 [45,46]. As one of miRNA-7's targets, UBE2A (ubiquitin conjugating enzyme E2A) is important in removal of amyloid peptides, and has been reported to be involved in several neurological diseases, such as AD [47,48]. These excess miRNA-7 thereby significantly reduce the translation of UBE2A mRNA. Subsequently, loss of UBE2A lead to accumulation of waste products, such as amyloid peptides and senile plaque, in AD brain cells. These data indicate that deficits in "circRNA-microRNA-mRNA" system may present an important reason of widely observed change of gene expression in AD. Interestingly, alternative splicing patterns have been reported to change in AD, and the expression of circular RNAs are significantly altered in AD-affected brain cells genome-widely [49–52]. For example, there 444 circular RNA were significantly upregulated, while 111 circular RNAs were downregulated in the hippocampus of AD rats compared to sham control groups [51]; RNA sequencing analysis of human brain astrocytes by Sekar *et al.* showed that there were over 2000 circular RNAs were uniquely expressed in AD cohort [52]. On the other hand, from *Drosophila, C. elegans,* mice to human, some circular RNAs are evolutionarily conserved, and there is obvious trend that the expression of many circular RNAs increases with age [42,43,53], suggesting that circular RNAs may participate in aging and AD

pathogenesis, and represent a potential class of clinic biomarkers and therapeutic targets.

Circular RNA in Neuropsychiatric Disorders

As mentioned above, ciRS-7 is a conserved circular transcripts that is highly enriched in animal brains but lowly expressed in other organs. CiRS-7 has also been found to have partially complementary target sites for miRNA-7 and near perfect binding sites for miRNA-671, but whether ciRS-7 inhibits or protects miRNA-7 might depend on the cellular context [45,46,54–57]. Indeed, Piwecka *et al.* have beautifully demonstrated that ciRS-7 is important for sensorimotor gating and synaptic transmission [55]. To explore the roles of ciRS-7 in brain, loss-of-function mutant mice was generated by removal of ciRS-7 locus. Interestingly, miRNA-7 expression decreased, whereas miRNA-671 expression increased in ciRS-7 KO brain. It is important to note that these two microRNAs were unaffected in other tissues of ciRS-7 KO mice, suggesting a specific and posttranscriptional regulation of circular RNA-microRNA axis in brain. Subsequently, as targets of miRNA-7, immediate early genes that have roles in neuronal activities were significantly upregulated globally, thereby leading to dysfunction of excitatory synaptic transmission. Behavioral assays confirmed that mice with depletion of ciRS-7 showed deficits in prepulse inhibition of the startle reflex. Taken together, Piwecka *et al.* have proved that ciRS-7-microRNAs-target mRNAs axis is important in neuropsychiatric disorders [55]. However, a following study by Kleaveland *et al.* have clearly showed that the Cyrano long noncoding RNA can induce accumulation of ciRS-7 by reducing miRNA-7 levels. Without Cyrano, excess miRNA-7 causes cytoplasmic degradation of ciRS-7 in neurons, in part through enhanced slicing of ciRS-7 by miRNA-671. The results by Kleaveland *et al.* suggest a regulatory network formed by the Cyrano long noncoding RNA, ciRS-7, miRNA-7, and miRNA-671 [54].

Circular RNA in Other Brain Disorders

(i) ***Memory***: PAIP2 has been reported as a pivotal translational regulator of synaptic plasticity and memory via poly(A)-binding protein (PABP) reactivation [58,59]. Nuclear circPAIP2 (exon-intron circular RNA) can regulate PAIP2 gene transcription in *cis* [10], thereby affecting memory development. (ii) ***Major depressive disorder***: circular RNAs have also been shown to be correlated with major depressive disorder (MDD) [60,61]. Among circular RNAs with varying expression in MDD patients, only hsa_circRNA_103636 expression was significantly rescued after 8-week antidepressant regimens, suggesting that hsa_circRNA_103636 can be an ideal biomarker for the diagnosis of MDD [60]. (iii) ***Multiple sclerosis***: current researches have demonstrated that the levels of several circular RNAs were significantly affected in multiple sclerosis cases. For example, Gasdermin B (GSDMB) circular RNA was found to be upregulated [62], whereas circ_0005402 and circ_0035560

were reported to be underexpressed in multiple sclerosis patients [63]. Thus circular RNAs could be also used as biomarkers for the multiple sclerosis [62,63].

PERSPECTIVES AND MOVING FORWARD: CIRCULAR RNAS AS PROMISING BIOMARKERS FOR HUMAN DISEASE

As a special class of non-coding RNAs, circular RNAs have caught many researchers' attention, and triggered a number of exciting studies. Thousands of circular RNAs (including exonic, intronic, and exon-intron circular RNAs) have been identified across species by a variety of RNA-seq data, and some of them have been reported to impact normal and disease states, including cancer, cardiovascular disease, neurological disease, diabetes and so on [64–71].

Because (i) many circular RNAs have been clearly reported to be expressed in a tissue- or development stage-specific manner, (ii) the stable structure and natural nuclease-resistance are the common features of most circular RNAs, circular RNAs can serve as a novel class of biomarkers for diagnostics and a potential therapeutic targets. For example, lung cancer (LC) is one of the leading causes of death worldwide, but there is not an ideal blood biomarker for LC so far. Recent studies revealed that the levels of certain circular RNAs (e.g., has_circ_0013958, hsa_circ_0000064 and hsa_circRNA_103809) were drastically increased in lung cancer tissues. Depletion of these circular RNAs significantly suppressed lung cancer cell proliferation and invasion [72–74], indicating that they could be used for not only the novel targets in LC therapy but also the blood biomarkers in LC early detection.

But it is important to point out that there are still several issues need to be addressed prior to the application of circular RNA biomarkers in clinical therapy. (i) ***Reliability and sensitivity***: because the clinical biomarker studies related to circular RNAs are still very limited, and the functions of most circular RNAs are still unknown, further experiments need to be employed to confirm the reliability and sensitivity of these potential biomarkers. (ii) ***Cost***: A low-cost approach that is used to detect circular RNAs in blood cells or exosomes need to be explored, because detection of circular RNAs in these samples is very expensive and time-consuming currently. In conclusion, circular RNA biology represents a novel and promising field in current medicine, biomarker and clinical researches.

AUTHOR CONTRIBUTIONS

RJ, ZL, and CH wrote the paper. RJ contributed to the figures in the paper.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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