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Circular RNA: a new star in neurological diseases

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Circular RNAs (circRNAs) are novel endogenous non-coding RNAs characterized by the presence of a covalent bond linking the 3′ and 5′ ends generated by backsplicing. In this review, we summarize a number of the latest theories regarding the biogenesis, properties and functions of circRNAs. Specifically, we focus on the advancing characteristics and functions of circRNAs in the brain and neurological diseases. CircRNAs exhibit the characteristics of species conservation, abundance and tissue/developmental-stage-specific expression in the brain. We also describe the relationship between circRNAs and several neurological diseases and highlight their functions in neurological diseases.

**Keywords:** circular RNAs; non-coding RNAs; microRNA sponge; microRNA; neurological diseases
1. Introduction

In addition to classic RNAs, the growing components of noncoding RNAs are circular RNAs (circRNAs). CircRNAs are a family of RNAs whose head 3′ and tail 5′ ends covalently bond together to result in a circular form. CircRNAs were first found in RNA viruses as early as the 1970s [1]. Unfortunately, only very few circRNAs have been serendipitously discovered during the past 30 years [2-4]. They were generally considered to be molecular flukes or products of aberrant RNA splicing due to their low levels of expression. Recently, with the development of high throughput sequencing technology and bioinformatics, circRNAs have gradually revealed their true colours.

Due to their ability to sequester microRNAs (miRNAs), circular RNAs play an important role in the fine-tuning of post-transcriptional gene expression. To the best of our present knowledge, only a small number of reviews have focused on summarizing the function of circRNAs in neurological diseases. Therefore, we review the characteristics of circRNAs in the brain and their functions in neurological diseases.

2. Biogenesis, Properties, and Functions of circRNAs

2.1 Biogenesis of circRNAs

Recent studies have demonstrated that the biogenesis of circRNAs is different from the canonical splicing of linear RNAs [5] and revealed four models of circRNA biogenesis. Model 1 is termed ‘lariat-driven circularization’ or ‘exon skipping’, which means that the splice donor at the 3′ end covalently splices to splice acceptor at the 5′ end and forms a lariat via exon skipping; then, the spliceosome removes introns, and circRNA is finally formed [6] (Fig. 1.1). Model 2 is termed ‘intron-pairing driven circularization’ or ‘direct backsplicing’, which means that two introns form a circular structure via base-pairing, and then introns are removed or retained to form circRNA or ELciRNA (exon–intron ciRNAs) [6] (Fig. 1.2). Furthermore, the reversed complementary sequences including inverted repeated Alu pairs are important for model 2 [5, 7-10]. Model 3 refers to the formation of circular intronic RNAs (ciRNAs) derived from introns [11]. The consensus motif containing a 7-nt GU-rich element near the 5′ splice site and an 11-nt C-rich element near the branch point site are minimally sufficient for an intron to escape debranching and degradation, and a 3′ ‘tail’ downstream from the branch point is trimmed to result in a stable ciRNA [11] (Fig. 1.3).

The fourth model of circRNAs’ biogenesis is that RNA-binding proteins (RBPs) bridge two flanking introns close together to provoke the formation of circRNAs, and then the introns are removed to
form circRNA [12] (Fig. 1.4). For example, the muscle-blind protein (MBL) acts as RBP in promoting circMbl biogenesis. Lately, researchers have demonstrated that RBPs may serve as activators or inhibitors of the formation of circRNAs in some conditions, such as RBP Quaking and RNA-editing enzyme ADAR1 [9, 13].

The four models are not equal. Some evidence indicates that intron-pairing-driven circularization might occur more frequently than lariat-driven circularization [14]. Although exon skipping, direct backsplicing and binding sites for specific RBPs may support circularization, the biogenesis of circRNAs is still not fully understood. Great efforts are still needed to determine how to regulate circRNA expression and whether there exist other ways to generate circRNAs.

2.2 Properties of circRNAs

According to recent studies, there are several remarkable properties of circRNAs as follows. First, circRNAs have incredible diversity. They are encoded by various genes of different sizes and expression levels, with different sized introns flanking the backsplice sites. A gene that gives rise to a circRNA could encode a single isoform or many [5, 15]. Second, these circRNAs have covalently closed loop structures with neither 5′–3′ polarity nor a polyadenylated tail, which makes them much more stable than linear RNA and insusceptible to degradation by RNA exonuclease or RNase R [16]. For example, more than 400 circRNAs were identified in human cell-free saliva [17]. Third, circRNAs can be found in many species, such as mice, C. elegans, Drosophila, plants, yeast, and protists [18, 19]. Nearly 2000 circRNAs have been predicted in mouse sequences and over 700 in C. elegans [19]; their existence may be a ubiquitous feature [6, 15, 19, 20]. Fourth, circRNAs are evolutionarily conserved between different species [6, 15, 18]. For example, genes encoding circles in one species are more likely to encode circles in other species [6, 15]. Intriguingly, Jeck et al. identified 69 circRNAs that contained precisely conserved backsplice junctions between mice and humans [6]. CircRNAs of humans and mice are often generated not only from orthologous genes but also from orthologous exons [20]. Fifth, circRNAs often have tissue/developmental-stage-specific expression. For example, circMyst4, circKlhl2 and circAagab were dramatically increased during brain development [21]. Hsa-circRNA 2149 has been detected in CD19+ leukocytes but not CD34+ leukocytes, neutrophils or HEK293 cells [19]. Some nematode circRNAs seem to be expressed in oocytes but are absent in 1- or 2-cell embryos according to sequencing data [19]. Sixth, the majority of circRNAs are endogenous noncoding RNAs, but only a small portion of exogenous circRNAs,
such as Hepatitis δ (HDV) and engineered circRNAs with internal ribosome entry sites (IRESs) can be translated [2, 22, 23].

2.3 Functions

2.3.1 CircRNAs function as competing endogenous RNAs or miRNA sponges

By far, our understanding of circRNAs’ functions is just the tip of iceberg, but two previously identified circRNAs, ciRS-7/CDR1as and circRNA Sry, were demonstrated to serve as miRNA “sponges” or potent competitive endogenous RNAs (ceRNAs) [19, 24-26] to sequester miRNAs and prevent the interactions between miRNAs and their target mRNAs [27].

Many studies demonstrated that circRNA ciRS-7/CDR1as can modulate the activity of the associated miR-7 [19, 24, 28-30]. Subsequent research has revealed that ciRS-7/CDR1as contains over 70 conserved seed matches for miR-7 and is densely Ago-protein-bound (Argonaute protein) [19, 24]. Importantly, the seed matches are limited in complementarity, thereby preventing ciRS-7/CDR1as from degradation from the bound miR-7 [24]. The silencing of ciRS-7/CDR1as decreases the expression of published miR-7 target genes [19, 24]; meanwhile, the overexpression of ciRS-7/CDR1as strongly suppresses miR-7 activity and increases the expression of miR-7 target genes [24]. Moreover, CDR1as is expressed at higher levels in nervous tissue. The overexpression of CDR1as in zebrafish embryos results in reduced midbrain size and mimics the phenotype of miR-7 loss-of-function, which causes morphological defects in the midbrain [19]. Another study showed that the circRNA Sry contains 16 miR-138 target sites and also likely functions as a miRNA sponge to sequester miR-138 and prevent the interactions between miR-138 and its target mRNAs [24]. In addition to ciRS-7/CDR1as and circRNA Sry, Li et al. recently detected that cir-ITCH spanned several exons of the E3 ubiquitin protein ligase and acted as a sponge of miR-7, miR-17 and miR-214 [26].

However, several analyses of the large set of exonic circRNAs identified by CircleSeq suggest that very few circRNAs in mammalian cells contain more than ten binding sites for an individual miRNA. Jeck et al. suggest that many exonic circRNAs only contain smaller numbers of putative miRNA binding sites [14]. Though circRNAs from the repeat-rich C2H2 zinc finger gene family have been found to have many miRNA sites, few circRNAs exhibit a greater capacity to serve as miRNA sponges [20]. You et al. found that brain circRNAs do not exhibit a greater capacity to serve as miRNA sponges than linear mRNAs [21]. Therefore, it needs to be clarified further whether
circular miRNA sponges are a general phenomenon and how networks of circRNAs, miRNAs and circRNAs maintain balance to regulate cellular homeostasis.

2.3.2 Circular RNAs can also function as protein sponges

With regard to this aspect, the circMbl derived from the mbl locus in Drosophila harbours binding sites for the MBL itself [31]. MBL acts as an RBP to induce circMbl production. The generation of circMbl consequently renders the pre-mRNA non-productive and limits the further production of the MBL protein. CircMbl tethers and decoys MBL, which prevents the further generation of circMbl and instead reactivates productive mbl mRNA production. Therefore, circMbl seems to be an intricate entity of an MBL auto-regulatory circuit. Furthermore, circMbl also encompasses highly conserved miRNA binding sites [32] and could have multi-faceted roles in the Drosophila brain.

2.3.3 Other functions

CircRNAs can regulate the expression of the parental gene. Some circRNAs are abundant in the nucleus and interact with the polymerase II machinery and modulate host transcription activity in a cis-acting manner. For example, ci-ankrd52 largely accumulates to its sites of transcription, associates with elongation polymerase II machinery and acts as a positive regulator of polymerase II transcription [11]. Some E1ciRNAs, such as circEIF3J and circPAIP2, can enhance the transcription of their parental genes in a cis-acting manner using a specific interaction with U1 snRNA [33]. Similarly, circ-ITCH interacts with miR-7, miR-17, and miR-214 and may increase the level of ITCH [26]. Few circRNAs can be translated as mentioned above. CircRNAs could also modulate the stability of mRNA. For example, CDR1as was reported to enhance the expression of CDR1 by stabilizing the sense CDR1 mRNA [34] and mcircRasGEF1B positively regulates the expression of ICAM-1 through modulating the stability of mature mRNA of ICAM-1 [35].

3. Characteristics of circRNAs in the Brain and Functions of circRNAs in Neurological Diseases

3.1 Characteristics of circRNAs in the brain

Researchers deep-sequenced rRNA-depleted total RNA samples from different mouse tissues, including the brain, liver, lung, heart and testis, and found that circRNAs existed in all the tissues, and their abundance was clearly highest in the brain [21]. The similar result was also observed in flies [32]. Another group compared the human frontal cortex, thyroid gland, liver, and muscle and
found overall enrichment for circRNA expression in the nervous system [36].

Some studies displayed that circRNAs are not equally distributed in neuronal compartments [36]. You et al. compared the abundance of circRNAs in synaptoneurosomes or neuropil from the hippocampus to that observed in a whole hippocampal homogenate or a microdissected layer comprising primarily hippocampal neuronal somata and found that most circRNAs were indeed enriched in either or both of the two synaptic fractions [21]. Rybak-Wolf et al. also found that circRNAs were strongly enriched in synaptoneurosomes compared to the whole-brain lysate and cytoplasm on all expression cut-offs [36].

Some groups have demonstrated that the expression of circRNAs is developmentally regulated in neurons and the change of expression of circRNAs is independent of their host linear transcripts. Rybak-Wolf et al. examined 29 human/mouse RNA sequencing datasets from dissected brain tissues or neuronal-differentiated cell lines and found that some circRNAs are expressed dynamically and independently of their linear transcripts, which implied that the expression of circRNAs in the brain is regulated [36]. You et al. drew the parallel conclusion that circRNAs were developmentally regulated in the brain [21].

As conservation in evolution often implies functionality, many groups analysed the conservation of circRNAs sequences in vertebrates. They have found that exonic sequences around the circRNA head-to-tail junctions showed extremely higher conservation compared to splicing sites [21, 36]. But, circRNAs displayed large differences among the different species. Guo et al.’s study showed that 20% of mouse circRNAs were detected in human cell lines [20]. This observation was in line with a recent study in which 23.6% of the circRNAs identified in mouse neuropil were also expressed in rat neuropil [21]. Furthermore, one study performed by Memczak et al. found only 4% of the mouse circRNAs were identified in human samples [19].

Because of the characteristics of species conservation, abundance and tissue/developmental stage-specific expression in brain, it is reasonable to presume that circRNAs are essential for the intact function of brain and may be regulators maintaining synaptic function. In addition, Rybak-Wolf et al. guess that circRNAs may be used by neuronal termini and molecular postsynaptic platforms as synaptic tags to keep a molecular memory due to their high stability and enrichment [36].

3.2 CircRNAs in neurological diseases

Studies show that circRNAs can influence gene transcription, mRNA splicing, RNA decay and
translation and participate in a wide range of biological processes. Considering the characteristics of circRNAs in brain, it is not surprising that dysregulated circRNAs can give rise to abnormal cellular functions and growth defects and are involved in neurological diseases (Table 1).

Recently, Lukiw provided initial evidence of a dysregulated miR-7-circRNA system in the sporadic Alzheimer’s disease (AD) hippocampal CA1 region by Northern blot hybridization techniques and the circularity-sensitive circRNA probe RNaseR and found that ciRS-7 was significantly reduced in AD patients compared with that in control tissues, and the deficits in ciRS-7 and ciRS-7 ‘sponging activities’ increased ambient miR-7 levels in AD patients’ brain cells [37]. The presence of up-regulated miR-7 may increase β-amyloid peptides excessively or/and result in tau protein hyperphosphorylation and ultimately lead to sporadic Alzheimer’s disease. Lukiw stated that it had a high likelihood of down-regulating AD-relevant targets, such as the ubiquitin protein ligase A (UPLA), which is essential in the clearance of amyloid peptides in AD [37, 51, 52]. Moreover, with a special analysis method, Julia et al. identified miR-138 as a potential molecular regulator of human memory function [53]. A recent study found that miR-138 is increased in AD models and it promotes tau phosphorylation by targeting the RARA (retinoic acid receptor alpha)/GSK-3β (glycogen synthase kinase-3β) pathway [38]. In contrast, an earlier study thought the increased miR-138 was associated with better memory by regulating acyl protein thioesterase 1 [39]. Therefore, circRNA Sry or miR-138 in AD should be further investigated.

This circRNA circMbl and its flanking introns contain conserved muscle-blind binding sites, which are strongly and specifically bound to MBL. The modulation of MBL levels strongly affects circMbl biosynthesis, and this effect depended on the MBL binding sites. When MBL is present in excess, circMbl can sponge out the excess MBL by binding to MBL [31]. The human orthologues of MBL are the muscle-blind-like proteins (MBNL1-3) that play an important role in myotonic dystrophy (dystrophia myotonica, DM) in humans, one of the most common lethal monogenic disorders of European descent. Upon the transcription of DM pathogenic genes, both the CUG and CCUG repeats fold into double-stranded stem-loops with the helices adopting a primarily α-form structure [40]. MBNL proteins act as splicing regulators to bind these stem-loop structures and lead to the sequestration of these important splicing factors in nuclear foci [41]. MBNL sequestration results in mis-splicing of various transcripts, several of which have been linked to symptoms observed in DM patients [42, 43]. Thus, circMbl may play a pivotal role in the nosogenesis of DM
via MBL/MBNL proteins.

Parkinson’s disease (PD) results from the progressive loss of dopaminergic neurons in the substantia nigra pars compacta. Five distinct genes have been identified to cause PD, including \( \alpha \)-synuclein, parkin, \( dj-1 \), \( pink1 \), and \( lrrk2 \) [54]. \( \alpha \)-Synuclein is the key player in the pathogenesis of PD based on genetic, neuropathologic, and cellular/molecular lines of evidence [55]. The over-expression of \( \alpha \)-Syn is associated with the impaired function of dopamine-generating cells and the development of PD. Loss of miR-7 in cultured PD cells possibly contributes to increased \( \alpha \)-Synuclein levels [44]. Additionally, miR-7 reduces \( \alpha \)-Synuclein expression dose-dependently and promotes the degradation of \( \alpha \)-Synuclein mRNA levels in HEK293T cells. Meanwhile, the silencing of CDR1as increases miR-7 activity and decreases the expression of published miR-7 target genes. So, Ghosal et al. predicted that CDR1as was associated with PD using bioinformatics [56]. A group of overlapping neurodegenerative disorders called \( \alpha \)-synucleinopathies, which includes PD, Parkinson’s disease dementia (PDD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and a number of less-well characterized neuroaxonal dystrophies [57]. Because CDR1as and miR-7 can regulate \( \alpha \)-synuclein, we can predict that CDR1as may also be involved in other \( \alpha \)-synucleinopathies besides PD.

Burd et al. discovered that circular antisense non-coding RNA in the \( INK4 \) locus (cANRIL) was an antisense transcript from the \( INK4A-ARF \) locus, and cANRIL expression correlates with the transcription of \( INK4/ARF \) and the risk of atherosclerotic vascular disease (ASVD) [45]. ASVD is an isolated risk factor of cardiovascular or cerebrovascular diseases. Therefore, abnormal cANRIL expression may be associated with cerebrovascular diseases.

Many studies have demonstrated that circRNAs participate in the carcinogenesis and the malignant behaviour of cancer, such as alimentary system carcinoma [58-61], breast cancer [62] and chronic lymphocytic leukaemia [63]. As ciRS-7 is expressed primarily in the brain, further expression analyses of various tumour-derived cell lines showed that it was also expressed in neuroblastoma and astrocytoma [64, 65]. Moreover, miR-7 can strongly reduce angiogenesis and tumour proliferation in a murine neuroblastoma tumour model with the local administration of miR-7 or the systemic administration of miR-7 in a mouse model with human glioblastoma xenografts [46]. Similarly, another group found that miR-7 was expressed at low levels in glioblastoma and can strongly inhibit glioblastoma xenograft growth in a mouse model by reducing the expression of
epidermal growth factor receptor (EGFR) [47]. Therefore, we can predict that ciRS-7 may be involved in the pathogenesis of malignant tumor in nervous system.

As previously mentioned, hsa-circRNA 2149 is supported by 13 unique head-to-tail spanning reads in CD19+ leukocytes but is not detected in CD34+ leukocytes, neutrophils or HEK293 cells [19]. We suppose that some circRNAs may have viral miRNA binding sites and therefore can affect immune responses. Recently, Dandan et al. used an miR-138 mimic or inhibitor to regulate its expression in CD4+ T cells and found miR-138 can balance the ratio of Th1/Th2 by targeting Runt-related transcription factor 3 (RTF3) [48]. CircRNA Sry can repress miR-138 activity. Another study found that circular RNA100783 may represent a novel biomarker for the longitudinal tracking of CD28-related CD8+ T cell aging and global immunosenescence [49]. All of these studies suggest that some circRNAs may be associated with inflammatory diseases or immune disorders in the nervous system.

In addition, researchers found the stable overexpression of the prion protein PrPc in HEK293 cells, which was shown to induce ciRS-7/CDR1as expression but not CDR1 [50]. Hence, PrPc could possibly be involved in the regulation of ciRS-7. In fact, we know very little of the relationship between ciRS-7 and prion disease. Therefore, we should unveil the relationship between ciRS-7 and prion disease in the future.

In fact, it lacks enough data to determine the exact role of circRNA in neurological diseases. We need to try our best to explore the relationship between circRNAs and neurological diseases and determine the possible role and mechanism of circRNAs in neurological diseases.

4. Conclusions

The research and application of circRNAs in neurological diseases are expanding. Besides the above-mentioned diseases, circRNAs are possible regulated in other neurological diseases because their special characteristics in brain, such as epilepsy. While new insights into circular RNAs have been rapidly generated, circRNAs provide a new understanding on the pathological mechanisms of the neurological diseases. CircRNAs provide new insights into targeted therapy due to their regulatory effects on genes. The ability of circRNAs to act as sponges of related miRNAs can be exploited as a novel technology to achieve gene regulation. We also predict that circRNAs in serum, plasma [66], saliva [17], exosomes[67] and cerebrospinal fluid will become new clinical diagnostic and prognostic biomarkers in neurological diseases due to their high circulating stability and
abundance. The research and application prospects for circRNAs in human disorders are promising.

The relationships between circRNAs and neurological diseases are still poorly understood due to a lack of firm and direct evidence; future studies should help contribute more to the body of evidence. In the near future, with the advancement of biotechnologies and basic studies, it’s hopeful that we disclose the physiological and pathological functions of circRNAs in neurological diseases and develop circRNA-based therapeutic strategies, allow safe and successful therapies in day-to-day clinical practice.

Authors’ contributions

Tao-Ran Li, MM: drafted and revised the manuscript for content, including medical writing for content. Yan-Jie Jia, MD: revised the manuscript for content. Qun Wang, MD: revised the manuscript for content, including medical writing for content. Xiao-Qiu Shao, MD: revised the manuscript for content, including medical writing for content. Rui-Juan Lv, PhD: drafted and revised the manuscript, including medical writing for content. All authors have seen and approved the final version of the manuscript.

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Disclosure

The authors declare that they have no conflicts of interest.

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PubMed PMID: 26138677.


Fig. 1. Biogenesis of circRNAs. (1) Exon skipping leads to mRNA consisting of exons (white) as well as a lariat structure containing the skipped exon (red). Due to the induced proximity between the splice donor at the 3’ end and the splice acceptor at the end, intralariat splicing involving these two splice sites has led to the generation of an EIciRNA and additional splicing produces circRNA. (2) Direct basepairing between the complementary sequence motifs in the introns flanking the exons results in a circRNA or EIciRNA. (3) The lariat intron is generated from the splicing reaction, a 7-nt GU-rich element (red line) near the 5’ splice site and an 11-nt C-rich element (yellow line) near the branch point site are minimally sufficient for an intron to escape debranching and degradation. (4) Interaction between RBPs facilitate the head-to-tail end-joining of introns flanking the exons.
<table>
<thead>
<tr>
<th>Diseases</th>
<th>CircRNA</th>
<th>Target</th>
<th>Possible mechanisms</th>
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<tbody>
<tr>
<td>AD</td>
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<td>miR-7</td>
<td>ciRS-7 is significantly reduced in AD patients and miR-7 may down-regulate AD relevant targets, such as the UPLA, which is essential in the clearance of amyloid peptides [37].</td>
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<td>Myotonic dystrophy</td>
<td>circMbl</td>
<td>MBNL1-3</td>
<td>MBNL proteins lead to sequestration of the stem-loop structures in nuclear foci and results in mis-splicing of various transcripts [40-43].</td>
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<tr>
<td>PD and other α-synucleinopathies</td>
<td>ciRS-7</td>
<td>miR-7</td>
<td>miR-7 reduces α-Synuclein expression dose-dependently and promotes the degradation of α-Synuclein mRNA levels [44].</td>
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<td>Cerebrovascular diseases</td>
<td>cANRIL</td>
<td>INK4/ARF</td>
<td>cANRIL expression correlates with INK4/ARF transcription and ASVD risk [45].</td>
</tr>
<tr>
<td>Nervous malignant tumour</td>
<td>ciRS-7</td>
<td>miR-7</td>
<td>miR-7 can strongly reduce angiogenesis and tumour proliferation in murine glioblastoma xenografts or neuroblastoma tumour model through reduced expression of EGFR [46, 47].</td>
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<tr>
<td>Nervous inflammatory diseases or immune disorders</td>
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<td>miR-138 can balance the ratio of Th1/Th2 via targeting RTF3 [48].</td>
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<td>circRNA100783</td>
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<td>CircRNA100783 may be involved in chronic CD28-associated CD8 (+) T cell aging [49].</td>
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<td>ciRS-7</td>
<td>miR-7</td>
<td>ciRS-7 expression was induced by the overexpression of prion protein PrPc [50].</td>
</tr>
</tbody>
</table>

**Notes:** AD: Alzheimer’s disease; PD: Parkinson’s disease; UPLA: ubiquitin protein ligase A; RARA/GSK-3β: retinoic acid receptor alpha/glycogen synthase kinase-3β; MBNL: muscle-blind-like proteins; cANRIL: circular antisense non-coding RNA in the INK4 locus; ASVD: atherosclerotic vascular disease; EGFR: epidermal growth factor receptor; RTF3: Runt-related transcription factor 3