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REVIEW ARTICLE

The novel roles of circular RNAs in metabolic organs

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Abstract Circular RNAs (circRNAs) with a covalently closed loop structure which was different with linear RNAs, recently re-merged as novel regulator and exerted function in multiple biological processes. Through deep RNA sequencing (RNA-seq) technology coupled with bioinformatic analyses, a number of circRNAs has been identified. Moreover, circRNAs exhibit tissue- and development-specific expression indicating their potential biological significance. Actually, function of circRNAs as miRNA sponge has been well demonstrated in some diseases, besides, circRNAs also could function as RNA binding protein sponge and regulate alternative splicing and gene transcription. Notably, Emerging evidences showed that circRNAs played a pivotal role on the development of diseases including atherosclerotic vascular disease, neurological disorders and liver diseases, and served as diagnostic or predictive biomarkers of some diseases. This review mainly discusses the current advance of circRNAs as regulator involved in many diseases, and highlights circRNAs which have been well elucidated biological and pathogenic mechanism.

Introduction

Different with linear RNAs terminated with 5′ caps and 3′ tails, circular RNAs are characterized by covalently closed loop structures where the 3′ and 5′ RNA ends are joined together.[1,2] This typical circular feature of circRNAs makes them much stable due to the capability of resistance to RNase R digestion.[3,4] Actually, circRNAs were discovered in RNA viruses in 1976, and generally considered to be byproduct of splicing and little biological function in the following years.[5–7] Until recent years, many research groups used high-throughput RNA sequencing technology coupled with bioinformatic analysis to identify a number of circRNAs and demonstrated the function of circRNAs in various organs. In addition, accumulating evidences indicated that the majority of circRNAs are abundant,

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conserved across species and often exhibit cell type or tissue-specific expression, suggesting that circRNAs have potential regulatory roles.[8–10]

Although any loci of genome has the possibility of producing circRNAs, majority of them mainly derived from regions of protein coding genes. Generally, three types of circRNAs can be cataloged including exonic circRNAs(e-circRNA) from exons, intronic circRNAs(ciRNAs) from introns, and retained-intron circRNAs(ElciRNAs) from both.[11–15] Moreover, circRNAs could exert multiple functions depending on the different location. Most ecircRNAs tend to be cytoplasmic and act as miRNAs and RNA binding protein (RBP) sponge, inversely, EIciRNAs and ciRNAs predominantly localize in the nucleus and can regulate alternative splicing and gene transcription. Until now, the function of circRNAs acting as miRNAs sponge was well demonstrated in many studies.[16–18] For example, ciRS-7 (circular RNA sponge for miR-7) contains more than 70 selectively conserved miRNA target sites and strongly suppresses miR-7 activity.[19] Sry, a testis-specific circRNA, serves as a miR-138 sponge due to containing 16 binding sites.[19] Interestingly, a subset of circRNAs with open reading frames (ORFs) has been identified to have the capacity of translation.[20,21] Furthermore, circRNAs also can be modified with N6-methyladenosine (m6A) which promotes efficient initiation of protein translation.[22]

Canonical splicing is responsible for catalyzing pre-mRNA via removing introns and joining exons. However, unlike canonical linear RNAs splicing, back-splicing linked 3′ and 5′ end together to promote circularization.[23,24] Strikingly, the inverted repeat sequences or Alu elements in the introns flanking the exons, bringing the splice sites into close proximity to each other via base-pair, play a vital role for back-splicing.[14,25–27] In addition to cis-elements, trans-factors have been reported to regulate circRNAs biogenesis. For instance, muscleblind (MBL) could bind to its own pre-mRNA and promote circMbl production.[23] Quaking (QKI) positively regulated formation of circRNAs during epithelial to mesenchymal transition, inversely, adenosine deaminase 1 acting on RNA (ADAR1) destabilizes the base-pairing and further suppressed circRNAs biogenesis.[28,29] Therefore, the expression of circRNAs exhibiting cell type or tissue specificity may be due to the combination control of circRNAs biogenesis by cis-elements and trans-factors in corresponding cells and tissues.[30] (See Fig. 1).

Recently, emerging evidences indicated that circRNAs played an important role on the development of metabolic diseases. In this review, we summarized studies concerning the discovery and functions of circRNAs in the metabolic organs including liver, heart, muscle and pancreas, and highlight the circRNAs which have been demonstrated to involve in the development of diseases, such as

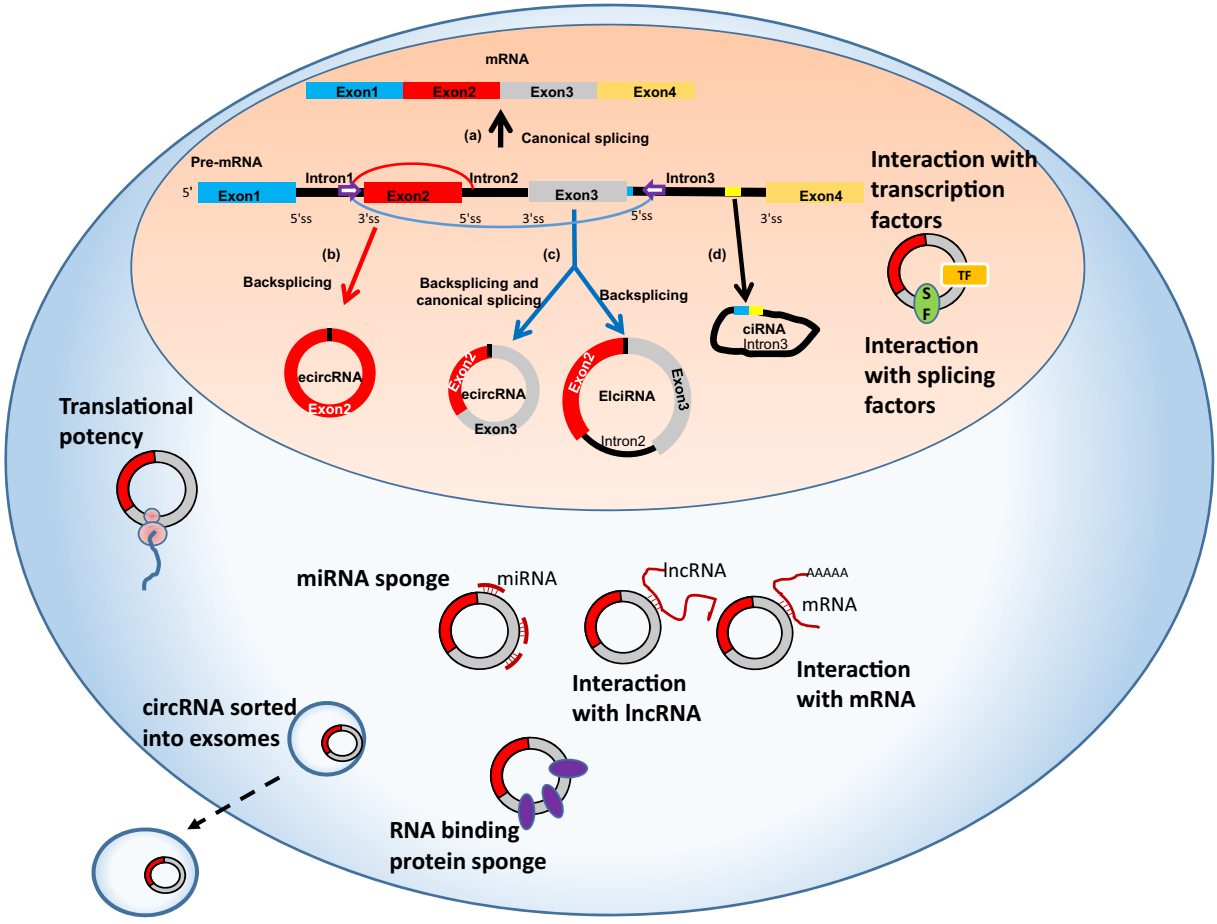

Figure 1 The biogenesis and functions of circRNA.

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