Experimental Cell Research 346 (2016) 248–254

Contents lists available at ScienceDirect

Experimental Cell Research

journal homepage: www.elsevier.com/locate/yexcr

Review article

Circular RNAs and systemic lupus erythematosus

Lian-Ju Li [1], Qing Huang [1], Hai-Feng Pan, Dong-Qing Ye *

Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei 230032, Anhui, China

ARTICLE INFO

Article history:
Received 31 March 2016
Accepted 20 July 2016
Available online 21 July 2016

Keywords:
Circular RNAs
MiRNA
Noncoding RNAs
SLE
Autoimmune disease

ABSTRACT

Circular RNAs (circRNAs) are a large class of noncoding RNAs that form covalently closed RNA circles. The discovery of circRNAs discloses a new layer of gene regulation occurred post-transcriptionally. Identification of endogenous circRNAs benefits from the advance in high-throughput RNA sequencing and remains challenging. Many studies probing into the mechanisms of circRNAs formation occurred cotranscriptionally or posttranscriptionally emerge and conclude that canonical splicing mechanism, sequence properties, and certain regulatory factors are at play in the process. Although our knowledge on functions of circRNAs is rather limited, a few circRNAs are shown to sponge miRNA and regulate gene transcription. The clearest case is one circRNA CDR1as that serves as sponge of miR-7. Researches on circRNAs in human diseases such as cancers highlight the function and physical relevance of circRNAs. Given the implication of miRNAs in the initiation and progression of systemic lupus erythematosus (SLE) and the roles of circRNAs in sponging miRNA and gene regulation, it is appealing to speculate that circRNAs may associate with SLE and may be potential therapeutic targets for treatment of SLE. Future studies should attach more importance to the relationship between circRNAs and SLE. This review will concern identification, biogenesis, and function of circRNAs, introduce reports exploring the association of circRNAs with human diseases, and conjecture the potential roles of circRNAs in SLE.

Contents

1. Introduction . . . 249
2. Identification of circRNAs . . . 249
3. Biogenesis of circRNAs. . . . 249
   3.1. Canonical splicing mechanism and circRNA biogenesis . . . 249
   3.2. Sequence properties and circRNA biogenesis . . . 250
   3.3. Proteins regulating circularization . . . 250
   3.4. Co- or post-transcriptional biogenesis of circRNAs . . . 250
4. Function of circRNAs . . . 250
   4.1. CircRNAs as miRNA sponges . . . 250
   4.2. CiRNA promote transcription of parental genes. . . . 251
   4.3. EIciRNAs enhances transcription of parental genes . . . 251
   4.4. Production of circRNAs competes with canonical splicing . . . 251
   4.5. Translation potential of circRNAs . . . 252
5. CircRNAs and human diseases . . . 252
   5.1. CircRNAs and cancers . . . 252
   5.2. CircRNAs and other diseases . . . 252
   5.3. CircRNAs and SLE. . . . 252
6. Conclusion . . . 253
Funding . . . 253

* Corresponding author.
E-mail address: ydqahmu@gmail.com (D.-Q. Ye).
[1] These authors equally contributed to this study and should be considered co-first authors.

http://dx.doi.org/10.1016/j.yexcr.2016.07.021
0014-4827/

Declaration of interest . . . 253
References . . . 253

1. Introduction

It is well known that eukaryotic genes are subject to splicing which generates mature messenger RNA (mRNA) and alternative splicing generating multiple mRNA isoforms [1]. CircRNAs result from a non-canonical alternative splicing that joins a splice donor to an upstream splice acceptor and forms covalently closed loops without 5′ to 3′ polarity, 5′ capping, and 3′ polyadenylation [2,3]. These features confer circRNAs resistance to RNase R, an RNA exonuclease degrading linear RNA, and longer half-lives exceeding 48 h compared with half-lives of less than 20 h of linear transcripts [4]. CircRNAs predominantly locate in cytoplasm [2,4]. The majority of circRNAs are transcribed in the sense orientation, derive from exon, intron, untranslated or intergenic regions [5,6], and typically consist of 2–4 exons with or without introns retained [7–9]. According to the sequence contained in circRNAs, circRNAs can be divided into 3 groups: *exo*nic circular RNAs (ecircRNAs) exclusively composed of exon [4], ciRNAs deriving from intron lariats [6], and EIciRNAs containing both exon and intron sequences [10]. A group of genes are able to simultaneously produce multiple circRNAs [3,11,12]. RNA circularization is conserved in paralogous or orthologous genes, indicating evolutionary preservation of circRNAs production [4,7,8,12]. The abundance of circRNAs is about 5–10% that of their linear transcripts and the circular/linear ratio varies a lot in distinct cells [7,13]. Notably, recent studies show that hundreds of circRNAs are expressed at higher levels than their corresponding linear transcripts in humans and Drosophila [9,11,12]. These evidences challenge the long-held thoughts that circular RNAs are by-products of splicing errors or intermediates that escape from intron lariat debranching [14–17]. In fact, physical evidences showing the function of circRNAs in sponging miRNA and regulating gene transcription are reported [5,6,10,18,19], though the roles of most circRNAs are unknown.

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease, predominantly affecting young women with a female to male ratio of 9:1 [20,21]. SLE is characterized by complement consumption, chronic inflammation, and production of autoantibodies against a variety of self antigens [21]. The spectrum of its manifestations ranges from mild cutaneous lesions to severe damages of major organs including kidneys, lungs, heart, and brain [22]. Although the etiology of SLE remains unclear, the higher concordance of SLE in identical twins supports the genetic basis [23]. Besides that multiple genome-wide association studies have identified over 50 genes associated with SLE. But the limited effect-size of these risk loci in its heritability and incomplete concordance of lupus in monozygotic twins argue for the roles of environmental or epigenetic factors in SLE [23,24]. One typical epigenetic mechanism well recognized in SLE is gene regulation by miRNAs which are a subset of endogenous, noncoding RNAs of 19–25 bp in length and post-transcriptionally regulate gene expression by directing degradation of mRNA or suppressing translation of mRNA [25]. For example, lower miR-146a level contributes to abnormal activation of type I IFN pathway in SLE patients and the elevated miR-30 is responsible for hyperactivation of B cells of lupus patients [26,27]. In spite of considerable progresses made in understanding of SLE during the past decades, there is still unmet need in the diagnosis and especially therapy of this condition. Considering the significance of miRNA in SLE and the role of circRNA as miRNA sponges, we conjecture that there may be some links between circRNAs and SLE and circRNA may be treatment target of SLE in future. In this review, we firstly introduce identification of circRNAs and then concentrate on the biogenesis, function of circRNAs, and their relationships with human diseases including cancers. At last, we envisage the potential roles of circRNAs in systemic lupus erythematosus.

2. Identification of circRNAs

The existence of circRNA in eukaryotic cells was firstly evidenced by electron microscopy in 1979 [28]. In contrast to the sporadic discoveries of a few circRNAs including DCC [29], ETS-1 [14], Sry [30], P-4502C18 [31], and MLL [32] over 20 years ago, recently thousands of circRNAs in Archaea, Drosophila, and human are reported, owing to the advent of biochemical enrichment strategies, computational approach, and deep sequencing [2,4,12,33,34]. For example, in one human fibroblast cell line treated with ribosomal RNA depletion and RNase R digestion, more than 25,000 circRNAs deriving from about 15% of transcribed genes are identified by mapping with MapSplice [4]. According to Julia Salzman and colleagues, circRNAs account for roughly 1% of the number of poly(A) RNA in human cells [7]. 15,849 and 65,731 circRNAs candidates are detected in mouse and human brain sample, respectively [12]. Yet, as the first step of analysis of circRNAs, it is important to point out that several problems pose great challenge to study of circRNAs and remain to be addressed. The five methods including TopHat-Fusion, MapSplice, find_circ, segemehl, and CIRI, exhibit different sensitivity and precision of detecting circRNAs [35]. The genome-wide identification of circRNAs may also be biased by different RNA-library treatments and the stringency level of parameter [4,35]. Appropriate methods should be applied to discriminate circRNAs with trans-splicing, genetic rearrangements, reverse transcriptase template switching, and tandem duplication [34,35].

3. Biogenesis of circRNAs

3.1. Canonical splicing mechanism and circRNA biogenesis

The widespread existence of circRNAs raises an immediate question: how these numerous circRNAs are produced? Until now, two models known as direct ‘backsplicing’ and ‘exon skipping’ have been put forward for possible mechanisms of circRNA production [4,34,36]. Though both mechanisms may operate in vivo, accumulating evidences suggest direct backsplicing may occur more frequently [2,4,34]. In direct ‘backsplicing’, a branch point firstly attacks the downstream 5′ splice site by its 2′-hydroxyl group, and thereafter the resulting 3′-hydroxyl end attacks the upstream 3′ splice site, forming a circRNA [4]. Canonical splicing signals immediately flank circularized regions [37]. By virtue of mutagenesis of expression plasmids, Liang et al. indicate that miniature introns composed of splice site and short inverted repeats are sufficient to make the intervening exons circularize in human cells [37]. Mutation of 3′ and 5′ splice sites affects gene circularization though with different consequences and mutating GU to CA in the 5′ splice site strongly reduces production of circRNAs from minigene [13,19]. The implication of canonical splice sites and spliceosomal machinery in circRNA biogenesis is further supported by the finding that treatment with splicing inhibitor