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Commentary

Biogenesis and ceRNA role of circular RNAs in skeletal muscle myogenesis

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ABSTRACT

Circular RNAs (circRNAs) are novel endogenous non-coding RNAs that are generated by reverse-splicing of precursor mRNA derived from various genes in mammals. Despite low expression, recent studies have shown that circRNA plays an important role in skeletal muscle myogenesis with competing endogenous RNA (ceRNA) functions. However, the potential regulatory role of circRNAs and interactions with miRNAs remain largely unexplored, and the function of circRNAs as miRNA sponges is not yet generally accepted. In this review, we outline the biogenesis and ceRNA mechanisms of circRNAs as well as their involvement in skeletal muscle myogenesis and discuss the conflicting conclusions of recent circRNA-ceRNA studies.

Introduction

In recent years, increasing evidence suggests a significant impact of non-coding RNAs on several molecular mechanisms. Unlike other linear products (microRNAs, small nucleolar RNAs, PIWI-interacting RNAs, and long non-coding RNAs), circRNAs are covalently closed RNA molecules and thus lack a 5′ cap and 3′ tail, which typically confer specific properties such as higher stability, RNaseR resistance, and longer half-lives (Chen and Yang, 2015). These circRNAs act in a tissue and developmental stage-specific manner, and numerous studies have verified gene regulatory functions of circRNAs in skeletal muscle development (Li et al., 2018a, Wei et al., 2017a, Li et al., 2018b, Legnini et al., 2017).

Vertebrates' skeletal muscle is an important and complex organ with a variety of functions, which are mostly derived from paraxial mesodermal somites and undergo hyperplasia and hypertrophy processes successively Buckingham et al., 2010; Guo et al., 2015. In general, myoblasts proliferate to increase cell numbers and fuse to form multinucleated myotubes, which then undergo further differentiation during embryogenesis, postnatal growth, and regeneration (CHARGÉ and RUDNICKI, 2004). Myogenesis has been widely studied during embryogenesis, in which a transcriptional hierarchy including MRFs (myogenic regulatory factors) and members of the MEF2 (myocyte enhancer factor 2) family precisely coordinate the activities of a set of muscle genes (Buckingham, 2006; Pownall, 2002). In addition, several non-coding RNAs have been identified in skeletal muscle and shown to be essential for skeletal muscle myogenesis at the epigenetic level Zhu et al., 2017a, Yu et al., 2017, Chen et al., 2006, Butchart et al., 2016. Recent studies have shown that several abundant circRNAs can function as miRNA sponges to alter effects on target mRNAs. There may or may not be ceRNA function of circRNAs, as most circRNAs expressed at low level rarely contain multiple binding sites for the same miRNAs (Guo et al., 2014). The precise molecular mechanisms of skeletal muscle myogenesis remain incompletely understood and the possible contributions of ceRNA function have not been fully described. Consequently, the goal of this review was to describe the state of knowledge about circRNA biogenesis and ceRNA function in relation to skeletal muscle myogenesis.

1. Biogenesis of CircRNAs

As a form of alternative splicing, back-splicing circularization is required for the formation of circRNAs, and requires splicing signals and spliceosomal machinery (AshwalFluss et al., 2014; Starke et al., 2015a). Based on their origin, circRNAs mainly fall into four categories: exonic circRNAs (ecircRNAs), exon-intron circRNAs (EIciRNAs), circular intronic RNAs (ciRNAs), and intergenic circRNAs (IcircRNAs), which are all produced from different circularizing mechanisms (Meng et al., 2016). The biogenesis of circRNAs is generally regulated by exon-containing lariats, cis-elements, and trans-factors that can bring the downstream 5′ splice donor and upstream 3′ splice acceptor site into close proximity (Salzman, 2016). However, the efficiency of back-splicing is lower than that of canonical splicing due to the steric challenge, and circularization and splicing of linear forms are competing processes (Zhang et al., 2016a). Recently, nascent circRNA were

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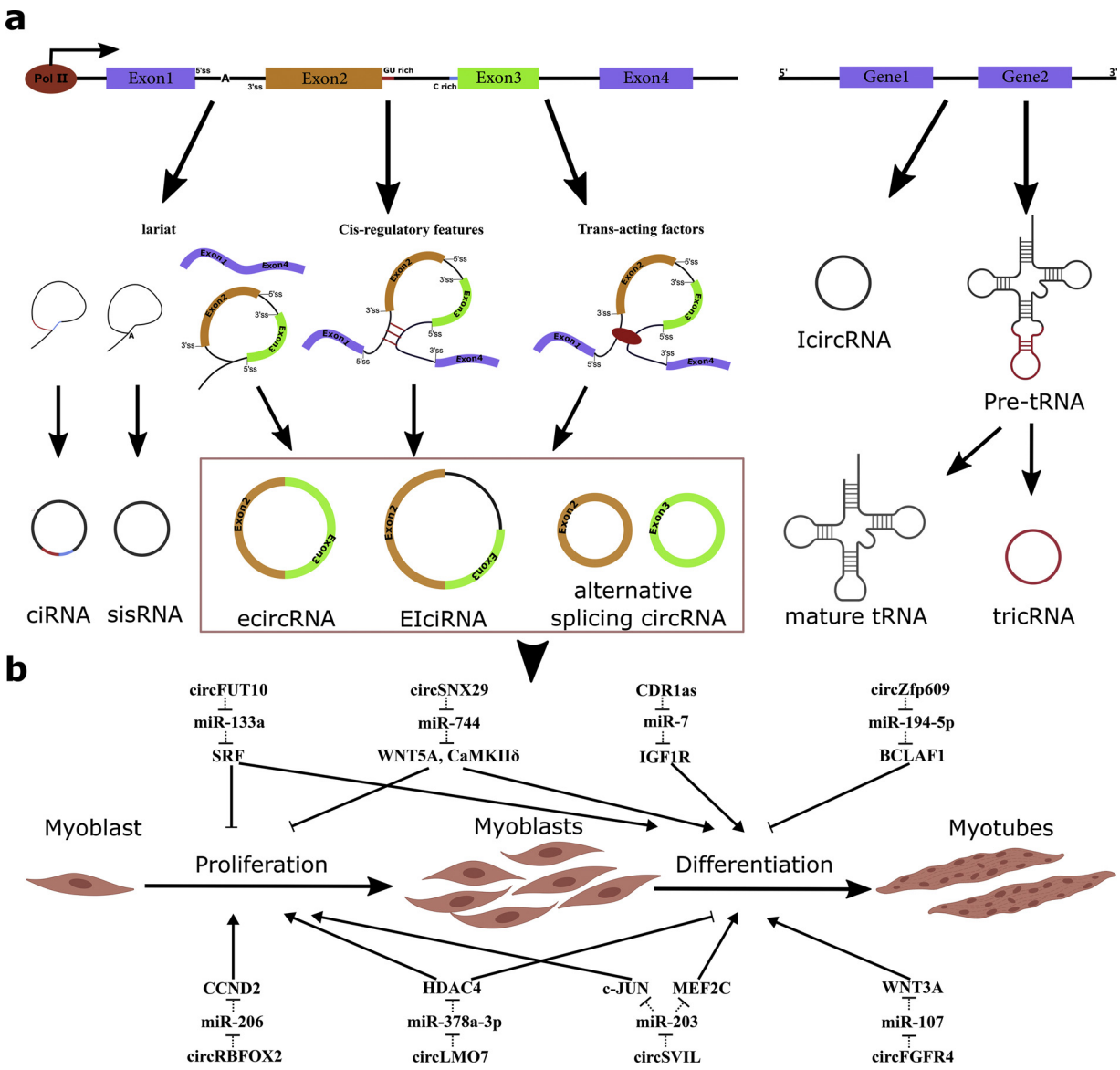

Fig. 1. Biogenesis of CircRNAs and the role of ceRNA in skeletal muscle myogenesis.
(a) Biogenesis of CircRNAs. The biogenesis of circRNAs is generally regulated by exon-containing lariats, cis-elements (RNA pairing across introns), and trans-factors (dsRBPs and ssRBPs) that bring the downstream 5′ splice donor and upstream 3′ splice acceptor site into close proximity. Accordingly, circRNAs are mainly classified into four categories: exonic circRNAs (ecircRNAs, including alternative splicing circRNA), exon-intron circRNAs (EIciRNAs), circular intronic RNAs (ciRNAs), and intergenic circRNAs (IcircRNAs). **(b)** Schematic representation of the ceRNA function of circRNAs in skeletal muscle myogenesis.

simultaneously detected with Pol II transcription, suggesting the potential that back-splicing to form circRNA can occur co-transcriptionally (Liang et al., 2017). Generally speaking, circRNA biogenesis is tightly regulated by factors that are specific for back-splicing and highly dependent on the biological environment (Fig. 1).

1.1. lariat-driven circularization

In canonical (linear) splicing, most eukaryotic introns are generally spliced out via the spliceosomal machinery, which consists of a series of specific proteins and five, small nuclear RNAs (Liang et al., 2017). During splicing, the 2′ hydroxyl of the branch point nucleotide adenosine attacks the 5′ splice donor site to form a lariat, and 3′ hydroxyl of the neighbouring exon then attacks the phosphodiester bond at the 3′ splice acceptor site to finally release the lariat intron. Remarkably, exons in an exon-containing lariat may undergo back-splicing and circularization to generate ecircRNA or EIciRNA molecules. Additionally lariat introns with GU-rich sequences near the 5′ splice site and C-rich sequences near the branch point can escape debranching and form ciRNAs (Barrett et al., 2015; Holdt et al., 2018). Recently, stable intronic sequence RNAs (sisRNAs), another kind of ciRNAs that originate from lariat introns and undergo 3′ -end trimming, have been suggested to regulate host gene expression (Pek et al., 2015). In addition, previous sequence analyses revealed the presence of IcircRNAs which exhibit a significant enrichment of conserved nucleotides, although the overall characteristics and biogenesis processes of these molecules are still unclear (Zhao et al., 2019).

1.2. Cis-regulatory feature-driven circularization

In general, back-splicing is limited by steric hindrance, but cis-regulatory elements located in introns flanking exons could relieve this steric hindrance. In the cis-regulatory model, RNA pairing across introns flanking exons can bring the distal splice site into close proximity followed by back-splicing of pre-mRNAs and exon circularization. For instance, although the exonic sequences in the GCN1L1 locus are highly

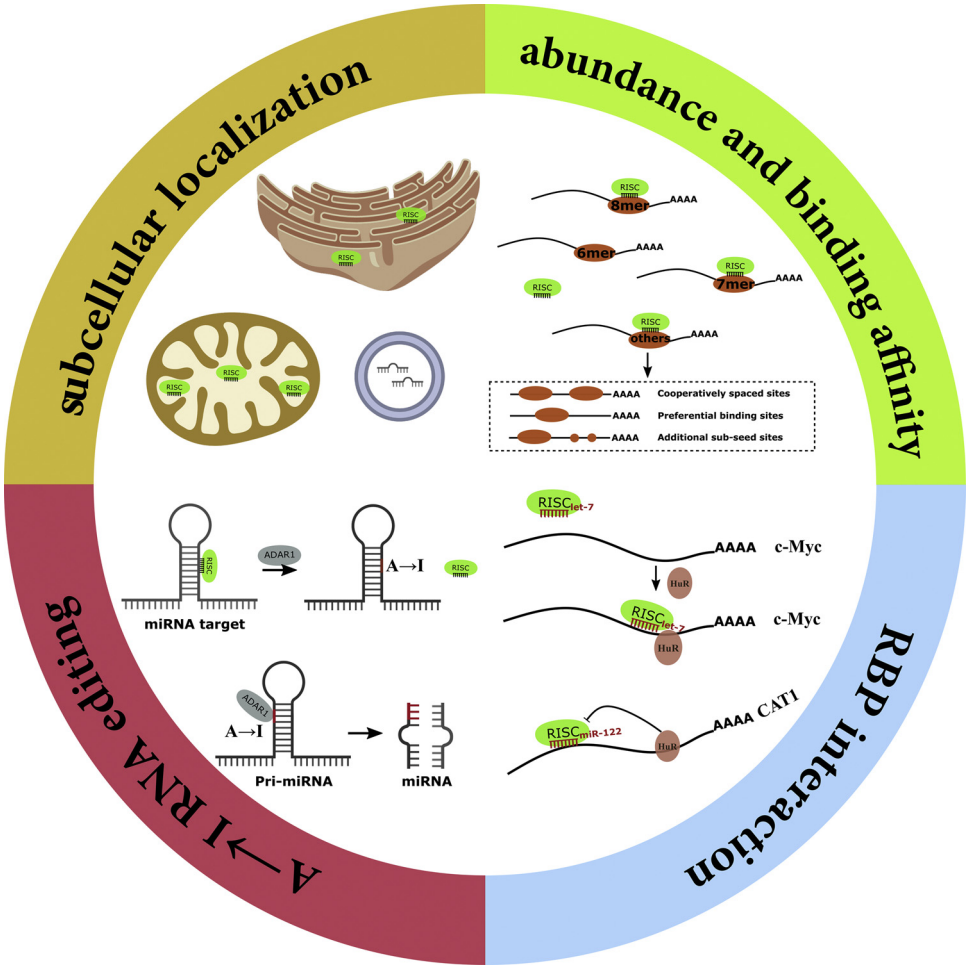

Fig. 2. Factors affecting ceRNA activity. The activity of ceRNA is affected by a series of factors, including the abundances of ceRNAs and shared miRNAs, binding affinity, RNA binding proteins (RBPs), RNA editing, and the subcellular localization of ceRNAs in physiological and pathological environments.

conserved between human and mouse, circGCN1L1 is detected in humans but rarely in mice, as RNA pairs are present in the human introns flanking exons but not found in the corresponding mouse locus (Zhang et al., 2014a). These RNA pairs are often derived from repetitive elements, such as Alus in primates, which belong to the short interspersed nuclear element (SINE) family and are highly abundant in the human genome (Prescott, 2011). Moreover, most mammalian pre-mRNAs contain multiple intronic repeats, and competition between complementary Alu elements may regulate alternative back-splicing (Tay and Pek, 2017). Alu elements are specific to primates, and circular RNA biogenesis in Drosophila is not driven by base-pairing interactions (Westholm et al., 2014). Intriguingly, although the same cis-elements are present, expression levels of circRNAs from the same loci are diverse in different cell lines and tissues, suggesting there may be other layers of regulation in circRNA expression.

1.3. Trans-acting factor-driven circularization

Accumulating studies suggested the involvement of trans factors in circRNA regulation. RNA binding proteins (RBPs) including double-stranded RBPs (dsRBPs) and single-stranded RBPs (ssRBPs) can regulate circRNA production by binding to specific RNA motifs (Zhang et al., 2016b, Starke et al., 2015b, Salzman et al., 2013). DsRBPs such as NF90 and/or NF110, DHX9, and ADAR1 directly bind to inverted repeat Alu elements (IRAlus) to negatively or positively regulate circRNA production (Salzman et al., 2013, Li et al., 2017a, Aktaş et al., 2017). In addition, ssRBPs like MBL and QKI bind to sequence motifs in the introns flanking exons to bring circularized exons closer via dimerization, resulting in circRNA formation (AshwalFluss et al., 2014; Conn et al., 2015). There is evidence that cis-regulatory features can cooperate with trans-acting factors to regulate back-splicing of the Drosophila Laccase 2 RNA, in which both intronic repeats, multiple hnRNP (heterogeneous nuclear ribonucleoprotein), and SR (serine-arginine) proteins act together (Kramer et al., 2015). Recently, another intronic circRNA, tRNA intronic circular (tricRNA), was discovered in archaea and animals, and its formation requires a bulge-helix-bulge (BHB) motif and many trans-acting factors including RtcB ligase and the tRNA splicing endonuclease (TSEN) complex (Noto et al., 2017). The molecular determinants of tricRNA biogenesis were elucidated using an tRNA splicing model in Drosophila and in a human cellular context (Schmidt et al., 2019).

1.4. CircRNA degradation

The mechanism of degradation of circular RNAs remains unclear, but miRNAs may initiate circRNA degradation by Ago2-mediated cleavage. For instance, the binding of miR-671 to CDR1 is fully complementary and conserved among vertebrates, and this binding directs miR-671-mediated CDR1as degradation by Ago2-Slicer-dependent cleavage (Hansen et al., 2014). However, it remains unknown whether other circRNAs are similarly vulnerable to miRNA-mediated cleavage. In addition, extracellular vesicles, including exosomes, can carry abundant cellular components such as lipids, proteins, and RNAs, and the secretion of these factors may be one mechanism to alleviate

circRNA accumulation (Lasda and Parker, 2016).

2. ceRNA hypothesis

Competing endogenous RNAs (ceRNAs) regulate other RNA transcripts by competing for binding to shared microRNAs via partially complementary sequences that are known as miRNA response elements (MREs), and induce the degradation of mRNA targets or repress translation at the post-transcriptional level (Salmena et al., 2011). Various ceRNAs have been discovered, including pseudogenes, mRNAs, lncRNAs, and circRNAs, which may interfere with the ability of miRNAs to actively adjust expression of their targets (Ling et al., 2013, Liu et al., 2014, Tay et al., 2011). As special endogenous non-coding RNAs, circRNAs typically have extremely abundant binding sites for microRNAs and can act as endogenous sponges. However, the extent of ceRNA networks and the molecular requirements for ceRNA cross-regulation remain unclear.

2.1. Factors affecting ceRNA activity

In recent years, theoretical models, bioinformatics, and cell biology approaches have been presented to describe the optimal conditions for ceRNA activity, and existing results suggest the activity of ceRNA is affected by a series of factors, including the abundances of ceRNAs and shared miRNAs, binding affinity, RNA binding proteins (RBPs), RNA editing, and the subcellular localization of ceRNAs in different physiological and pathological environments (Tay et al., 2014) **(**Fig. 2**)**. Several mathematical models show that the balance between miRNAs and ceRNAs is critical for ceRNA activity. According to the “target threshold effect” hypothesis proposed by Mukherji, optimal ceRNA interactions occur when the abundances of ceRNAs and miRNAs are nearly equal, and levels of miRNAs that are too high or too low relative to the levels of ceRNAs may reduce competition (Mukherji et al., 2011; Figliuzzi et al., 2013).

The ceRNAs may bind and sequester miRNAs with unequal efficiency, and the potential effectiveness of a ceRNA is closely related to the efficiency of miRNA targeting and repression. The most effective canonical site is an 8 mer site that comprises the “seed region” flanked by both the match at position 8 and the A at position 1, followed by 7mer sites (base pairing to “seed region” or nucleotides 2–7 with a Base A at position 1) and then poor efficiency 6mer sites (base pairing to only nucleotides 2–7 of the miRNA) (Lewis et al., 2005). These site types with different efficiencies determine the effectiveness of miRNA repression, which in turn also determine the overall effectiveness of the respective ceRNA (Denzler et al., 2016). Recently, the binding affinity between ceRNAs and miRNAs has been shown to be guided by the number and location of these site types, preferential binding sites, and even the presence of additional sub-seed sites, making the assessment of ceRNA potential increasingly complex (Werfel et al., 2017, Grimson et al., 2007, Salomon et al., 2015). In addition, miRNA binding sites with extensive complementarity to the miRNA can trigger degradation of the miRNA rather than just competing with other miRNA-binding sites; these binding sites are the most effective site types but may be rare in mammals (Ameres et al., 2010, Bartel, 2009). Thus, the ability of transcripts to act as ceRNA depends on not merely the total number and identity of all miRNA binding sites, but also the number of binding sites present for a particular miRNA.

Binding affinity is not to be the only factor determining miRNA-mediated target repression, and RBPs can directly occupy RNA target sites or alter the secondary structure of RNA to affect the accessibility to miRNAs. HuR, an RBP with affinity for AU-rich mRNAs, may promote the targeting of let-7-loaded RISC to an adjacent region of the c-Myc 3′UTR that is AU-rich, in which HuR binding perhaps changes the local RNA conformation to unmask the let-7 recognition site (Kim et al., 2009). In contrast, the miR-122-mediated repression of CAT-1 could be reversed by the binding of HuR to the 3′UTR of CAT-1 mRNA (Bhattacharyya et al., 2006). Furthermore, HuR can directly bind to miR-16 to prevent its interaction with the COX-2 3′UTR (Young et al., 2012). Recently, circAGO2 was discovered to physically interact with HuR to promote its enrichment on the 3′-UTR of target genes, exerting steric hindrance effects which limit the functions of AGO2-miRNA complexes, resulting in repression of AGO2/miRNA-mediated gene silencing (Chen et al., 2018). AGO2 phosphorylation may inhibit target mRNA binding, and RBPs may regulate the Ago2 phosphorylation cycle, but a RBP capable of this activity has not been found (Golden et al., 2017).

As a form of post-transcriptional processing, the editing of miRNAs and targets may both affect ceRNA activity. For instance, targeted by ADARs, 16% of human pri-miRNAs may undergo adenosine to inosine (A→I) RNA editing, which can interfere with both miRNAs processing and the miRNA-mediated gene silencing (Takeuchi et al., 2008). In addition, previous experimental and computational analysis suggested that greater than 85% of pre-mRNAs are subject to A-to-I RNA editing, with most target sites located in introns and UTRs (Athanasiadis et al., 2004). These phenomena may visibly increase the complexity of ceRNA interactions.

Most miRNA-target interactions occur in the cytoplasm, where pre-miRNAs are processed into mature miRNAs, however, whether these interactions normally occur throughout the cytoplasm or within specific cytoplasmic regions is unclear. A previous model showed miRNA-loaded AGO2 significantly co-located with rough endoplasmic reticulum (rER) membranes, leading to the efficient repression of mRNA that contain miRNA binding sites (Stalder et al., 2014). In addition, miRNAs have been detected in other membrane-bound compartments, such as secreted vesicles and mitochondria (Zhang et al., 2010; Zhang et al., 2014b). The subcellular localization of RISC components likely can affect the extent of miRNA-mediated repression and thus the potential for ceRNA crosstalk.

2.2. CeRNA hypothesis controversy

The ceRNA hypothesis remains controversial because there is no plausible explanation for how a change in expression of individual miRNA targets could influence enough miRNA molecules to affect other targets. A better understanding of the molecular specificity and dynamics of miRNA-mediated target repression is necessary to resolve this ceRNA controversy. The expression of individual miRNA targets constitutes only a tiny fraction of the cellular target-site abundance that affect the activity of miRNAs, and recent mathematical models to investigate the stoichiometry between miRNAs and their target sites concluded that ceRNA crosstalk is efficient when the ceRNA is equimolar to its mediating miRNA (Ala et al., 2013; Hausser and Zavolan, 2014). However, these mathematical models did not illuminate a connection between the relative abundances of various RNAs and physiological ceRNA crosstalk (Smillie et al., 2018). Even so, the stoichiometric relationships between miRNAs and their target sites were investigated experimentally, and two models of miRNA targeting have been proposed. In the ”hierarchical affinity model”, miRNAs preferentially bind 8mer sites rather than 7mer or 6mer sites. Accordingly, within a physiological range, the ceRNA can provide sufficient miRNA binding sites to cause the derepression of other miRNA-targets, but only for miRNAs with a low or intermediate miRNA-target ratio (Bosson et al., 2014). In the “mixed-affinity model”, sites of all different affinities contribute to the overall effective target abundance, regardless of the miRNA level, which suggests that an equivalent number of miRNA binding sites must be provided by the ceRNA to alter the repression of miRNA targets (Denzler et al., 2016). The key difference between the two models is the effect that miRNA abundance has on the potential for ceRNA crosstalk, and in consideration of the fact that changes in ceRNAs must approach a miRNA's target abundance before they can exert a detectable effect on gene regulation (Ludwig et al., 2016). Thus, some researchers concluded that ceRNA crosstalk is not possible within

a physiological range of transcript abundance (Denzler et al., 2016). Despite the controversy surrounding the ceRNA hypothesis, the experimental evidence in general supports the notion that ceRNA crosstalk can be physiologically relevant. As a plausible generic mechanism to regulate gene expression, the ceRNA hypothesis has been widely considered and has stimulated several new areas of research (Thomson and Dinger, 2016).

3. ceRNA function of circRNAs in skeletal muscle myogenesis

Despite the controversy surrounding the ceRNA hypothesis, large amounts of experiment results showed that ceRNA crosstalk can be relevant to myogenesis, and lncRNAs have been identified as potent regulators of myogenesis (Zhu et al., 2017b, Song et al., 2018, Liang et al., 2018). However, the ceRNA functions of circRNAs in skeletal muscle myogenesis remained elusive. Using high throughput sequencing, our team reported the first analysis of circRNA landscape at different stages of bovine skeletal muscle myogenesis, and subsequent functional research indicated that circRNAs play an important role on skeletal muscle myogenesis by acting as ceRNAs to sequester specific miRNAs. For instance, bovine circLMO7 appears to function as a ceRNA for miR-378a-3p to promote proliferation and inhibit apoptosis and differentiation of myoblasts (Wei et al., 2017b); circFUT10 reduces proliferation and facilitates differentiation of bovine myoblasts by sponging miR-133a (Li et al., 2017b); circFGFR4 promotes myoblast differentiation by sponging miR-107 to maintain the expression of WNT3A (Li et al., 2018b); and circSNX29 serves as a miRNA-744 sponge to attenuate its inhibition of WNT5A and CaMKIIδ, inhibiting proliferation and facilitating differentiation of myoblasts (Peng et al., 2019). In the mouse myoblast cell line (C2C12), circZfp609 was reported to sponge miR-194-5p to relieve its inhibition of BCLAF1 and repress myogenic differentiation (Wang et al., 2018). During the differentiation of goat skeletal muscle satellite cells, increasing MyoD activated CDR1as by binding to its promoter in nuclei, resulting in accumulation of CDR1as in the cytoplasm. Moreover, CDR1as was showed to partly relieve insulin like growth factor 1 receptor (IGF1R) by competitively binding to miR-7, consequently activating muscle differentiation (Li et al., 2019). In chicken, two circRNAs produced by the RBFOX2 gene were found to promote the proliferation of myoblasts by binding miR-1a-3p and miR-206, and chicken circSVIL could promote the proliferation and differentiation of myoblasts to sequester the functions of miR-203 (Ouyang et al., 2018a; Ouyang et al., 2018b). Despite these recent advances in our understanding of circRNA ceRNA functions in skeletal muscle myogenesis, the post-transcriptional regulation of circRNA remains poorly understood. For instance, it is unclear whether circRNA back-splicing modes, spatiotemporal expression, protein binding, transcription complex interaction, cellular localization, or other factors affect its ceRNA function. The relatively few ncRNAs studies in skeletal muscle myogenesis have been mainly performed using tissue culture (in vitro). This approach is both convenient and informative, however, this approach may not be able to reveal the complex modulation of the extracellular matrix during skeletal muscle development. Most in vivo studies of ncRNA have been conducted with focus on the pathological state of mature muscles, such as atrophy and muscular dystrophies, but in vivo, the requirement of circRNAs in myogenesis in mammals has not been evaluated by careful, targeted deletions. Intriguingly, despite the positive effect of muscle-specific miRNAs such as miR-1, miR-133, and miR-206 in cultured skeletal myotubes, genomic ablation in mouse models showed no apparent effect on normal muscle development Zhao et al., 2007, Liu et al., 2008, Williams et al., 2009. Thus the role of circRNA in the ceRNA network for skeletal muscle myogenesis requires more comprehensive elucidation.

Perspectives

Research interest in the physiological and pathological effects of circRNA has grown in recent years, and the most reported circRNA function is acting as ceRNA. Here, we present an overview of circRNA biogenesis and its mechanisms of ceRNA functions in skeletal muscle myogenesis. The ceRNA hypothesis remains controversial despite the extensive relevance of ceRNAs network in both normal physiological conditions and pathophysiological states. Thus, a more nuanced view of ceRNA crosstalk should be considered. Models of ceRNA mechanism should not only account for the abundances and binding affinity of seed-matched target sites, but also consider effects of altered RISC activity, RBP interactions, and subcellular molecular co-localization. Studies of ceRNA functions of circRNA in skeletal muscle myogenesis remain in the initial stage, and there is insufficient evidence to conclusively demonstrate a physiologically relevant ceRNA mechanism. Hence, more methods to identify and characterize ceRNA function should be performed. For instance, AGO2-CLIP-Seq of primary myoblast cells may reveal direct binding of miRNA to circRNA; mutagenizing miRNA binding sites on circRNA by CRISPR in myoblast cells could be used to confirm miRNA-dependence of circRNA crosstalk, and creating mouse models with knockouts of proposed circRNA or with mutagenized miRNA binding sites could confirm ceRNA function of circRNA in vivo. In conclusion, greater insight into interactions of non-coding RNAs that regulate muscle growth and development may suggest methods for livestock industries to improve meat quality and production or treat clinical muscle disorders using molecular approaches.

Declaration of Competing Interest

The authors declare no conflict of interest

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