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CircRNA: Its biogenesis and role in skeletal muscle development

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Abstract

Previously, circRNAs considered splicing errors during transcription, but recent studies uncovered that circRNA is a new group of noncoding RNAs. CircRNAs are produced through back splicing of pre mRNA and have more stability than linear RNA due to its closed loop structure. Numerous studies have unveiled the regulatory functions of circRNA in various biological mechanisms. Current literature has observed that circRNAs regulate the myogenesis of skeletal muscles through sponging miRNAs or acting as competitive endogenous RNA (CeRNA). Apart from myogenesis, it also regulates the functioning of different proteins at the molecular level and plays a key role during translation or protein encoding. All these facts have opened a new arena of research regarding the regulation of gene expression. This study aims to discuss the research advancements and new developments in the regulatory functions of circRNAs, including the development of skeletal muscle. This study also intends to discuss some newly discovered circRNAs involved in skeletal muscle development, especially in chicken and cattle.

Keywords: Circular RNA; Myogenesis; Skeletal muscle; Gene expression

1. Introduction

With the ever-increasing human population, food security is becoming a challenge for humanity. FAO estimates that there are 820 million undernourished people; one in eight people still go to bed hungry each night (1). Agricultural innovation is an effective tool to tackle this situation. In livestock production, the skeletal muscles of food animals are a major source of human food. Muscle development or myogenesis is a multifarious process depending on the number of genetic factors and pathways (2). Muscle growth is a finely orchestrated process regulated by coding and noncoding RNAs. Myogenesis involves the proliferation and differentiation of Muscles. Many studies have revealed that circRNA plays a crucial role in myogenesis by regulating the development and growth of skeletal muscles in different animals, including cattle, chickens, and pigs (3, 4). Vertebrates' skeletal muscle is one of the essential organs with intricate regulatory mechanisms. Recently, many Noncoding RNAs have been discovered in skeletal muscles, and some studies revealed that noncoding RNAs are mandatory in order to carry out proper regulation of skeletal muscle myogenesis at the epigenetic level (5).

Although the existence of Circular RNA (circRNA) for the first time was uncovered in eukaryotic cells in 1979 but did not gather much attention from scientists, they thought it was junk DNA and had nothing to do with genetic regulatory mechanisms (6). Later it revealed that circRNA is a class of noncoding RNA. In contrast to linear RNA, circRNA has a closed loop structure. An explicit mode of alternative splicing produces circRNAs during the transcription process, known as back splicing, ignited by the spliceosomal mechanism (7,8). CircRNAs can be produced from exons or introns. Three types of RNA can be produced during back splicing, exonic, intronic, and exon-intron circRNA (9). However,

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circRNAs mainly arise from exons and known as exonic circRNA (10). Many eukaryotic protein-coding genes are responsible for the production of circRNA (11). Studies have revealed that circRNAs are evolutionally conserved, and their expression levels are tissue and developmental stage-specific, indicating that circRNAs can regulate functions (12). Interestingly, recent studies reveal that circRNAs are abundant in skeletal muscles and global expression levels of circRNAs dynamically change during myoblasts differentiation (13,14). In addition, several circRNAs have demonstrated vital roles in muscle development and growth. Here, this study will highlight recent advances in understanding circRNAs biogenesis and expression in skeletal muscle development, focusing on their function and mechanism.

1.1 Regulatory functions of circRNA

1.1.1 CircRNAs regulate gene expression by sponging miRNA:

The ability to behave as a miRNA decoy is the unique property of circRNA. Numerous evidence-based studies have reported that circRNA can regulate gene expression by sponging miRNA (15). Studies have shown that circRNAs have numerous binding sites for miRNA. The latest research revealed that circRNA effect miRNA through these binding sites. It is believed that miRNA binds to mRNA to regulate protein production and functioning. Therefore, recent studies have shown that circRNA indirectly affects the translation process by sponging miRNA (16). Many studies revealed that circRNA has a major say in gene expression and regulation up to a limited extent by controlling miRNA activity. CDR1as is the first circRNA discovered to have a sponging effect on miRNA. The study has reported that CDR1as has more than 70 binding sites for miR-7. CDR1as is responsible for sponging the effect of miR-7 to increase the level of respective mRNA (17).

Furthermore, the Y gene responsible for sex determination is responsible for producing circSRY. A recent study revealed that circSRY regulates the expression of miR-138 by behaving like ceRNA. It possesses 16 binding sites for miR-138 (18). Many circRNAs have binding sites for specific miRNAs target while some circRNA contain binding sites for different circRNAs (19). As circITCH, circHIPK3 and circCCDC66 act as a sponge for multiple miRNAs (20,21). Another circRNA named circTCF25 has binding sites for the number of miRNAs. It sponges the effect of miR-3A, 3P, and miR-107 (22).

Thousands of circRNA have been discovered to have a role in gene expression and regulation. However, still, research about circRNA is in its early stages. The main focus of studies regarding circRNAs is on the sponging effect on miRNA and manipulating RBPs.

1.1.2 Involvement of circRNA in translation

Different studies have uncovered the surprising fact that circRNAs also play their part during transcription and translation. Many circRNA have been found to affect the transcription process by enhancing their parent genes' transcription (23). They are only involved in the transcription of their parent genes. Zhang et al. found that many circRNAs produced from the introns of MCM5, SIRT7, and ANKRD52 are involved in the transcription of genes from which they originated. Research shows a decrease in the transcription of parent genes after knocking down of respective circRNA (23). This study has confirmed the effect of circular RNA in the transcription of some genes.

CircRNA regulates the transcription efficiency by making transcription complex with other transcription factors, including elongation pol II. Moreover, a decrease in parental gene miRNA levels has been observed after the knockdown of respective circRNAs. These circRNAs, together with U1 snRP and Pol II enhance the transcription of respective genes. It is also noted that the Knockdown of circRNAs blocks the transcription-enhancing effect (24). CircRNAs are present in both cytoplasm and nucleus. A circRNA derived from FLI 1 has been reported to regulate the transcription of FLI1 through methylation. It is evident from different studies that circRNAs enhance the transcription of their parent genes both through the epigenetic mechanism and transcriptional complex (7).

1.1.3 How circRNA modifies protein functioning

CircRNA also interacts with proteins and can sponge the functioning of protein through binding sites. CircRNA regulates gene expression by interacting with proteins. CircMBL is one of the circRNAs, which act as a protein decoy. circMBL has binding sites for respective proteins. Thus, MBL protein binds to CircMBL, which is necessary for the biogenesis of CircRNA (15,25,26).

Recent studies have also shown that circRNA is involved in protein functioning; it acts as a protein lure to regulate protein functioning. CircRNA forms a ternary complex for cell growth and survival, as circRNA forms a transcription complex by binding with pol II and U1 snRNP (27). CircRNAs arise from protein-coding genes in the back splicing

process, which, in turn, is parallel to the processing of linear mRNA. Some studies also explored the tempting idea that circRNAs are responsible for protein synthesis. It is also a general concept that circRNA regulates the protein functioning by interacting with RNA binding protein (28,29).

1.1.4 CircRNAs; encoding proteins

Various experiments revealed that circRNAs are covalently closed RNA molecules and are resilient to attack by exonucleases. Surprisingly, they belong to the noncoding RNA class; some are experimentally corroborated to code for protein products (30). A recent study on circFBXW7 provides a confirmatory indication that circRNA can encode functional protein in vivo. circ-FBXW7 encodes a novel 21-kDa protein corroborated by the internal ribosome entry site, the name of the respective protein encoded by circFBXW7 is FBXW7-185aa. Endogenous circRNA encodes a functional protein in human cells, and circ-FBXW7 and FBXW7-185aa have potential prognostic implications in brain cancer (31).

CircRNA is a class of RNA placed in Noncoding RNAs. It lacks cap and poly (A) structure, which is necessary for the proper translation. Still, some studies reported the role of circRNA in coding different proteins (31,32). It shows that circRNA also can code for proteins. An internal ribosome entry site is needed to translate circRNA into proteins. Translation of circRNA is dependent on IRES. Indeed IRES is responsible for the initiation of transcription; that is why circRNA expression vector containing IRES can be translated into proteins (33).

1.2 Role of circRNAs in skeletal Muscle development

Many studies show that circRNA is found in many other tissues, including the brain, heart, liver, lung, and skeletal muscles. circRNA's function is also found in the development of many diseases, including cancer. Many studies have reported that skeletal muscle is enriched with various circRNAs (13). According to a study, 2000 to 37000 circRNAs have been reported in skeletal muscles (34). Skeletal muscle is one part of the living body. In livestock production, skeletal muscle occupies an essential place. Due to its availability as human food, the ever-growing population burden on the planet demands more livestock production efficiency (35). It is estimated that many genes have the ability to produce more than one circRNA. A study reported that 36% of genes are responsible for the production of circRNAs, and 15% of genes have the potential to generate more than 10 circRNAs (13).

Recently circRNA has emerged as a regulator in the development of skeletal muscles. Numerous circRNAs have been discovered in the skeletal muscles of many species. It controls the various developmental and physiological conditions in skeletal muscles by participating in muscle differentiation and proliferation. The latest research in muscle development has shown the abundance, diversity, and dynamic expression of circRNAs (36).

CircRNA is both tissue and developmental stage-specific. Specific circRNAs are found in different tissue of the living body. These specific circRNAs only regulate the gene expression for respective tissues. Apart from tissue specificity, circRNA is also developmental stage-specific. Several circRNA is only expressed during a particular development stage. CircRNAs have also proved developmental stage-specific—for example, a study revealed that 57.2–63.9% of porcine skeletal muscle circRNAs were observed at only one developmental stage (4). In short, recent studies propose circRNAs are plentiful in skeletal muscle, conserved between species, and regulated in myogenesis and muscular disease.

1.3 CircRNA as competitive endogenous RNA during myogenesis

Myogenesis is the process of regeneration of skeletal muscles, as skeletal muscle cells have the potential to regenerate from satellite cells (37). Myogenesis is a highly complex process involving properly organized transcriptional machinery that coordinates the functioning of genes involved in muscle development. Current studies on muscle development have explored a new fact that noncoding RNAs are also involved in regulating muscle gene expression. However, there are many knowledge and research gaps regarding the proper mechanism and functioning of circRNA (38). The experiments have shown that circRNA plays a vital role during the myogenesis of skeletal muscles by behaving as ceRNA to inhibit the functioning of specific miRNAs. A circular RNA named circFUT10 is responsible for facilitating myoblast differentiation and reducing proliferation by blocking the specific functioning of miR-133a (35). Another circular RNA, circFGFR4, has been witnessed to work for the expression regulation of WNT3A (39).

During the study of skeletal muscle differentiation in goats, CDR1as binds to its promoter in nuclei, which in turn causes the accumulation of CDR1as in the cytoplasm. CDR1as discharges insulin-like growth factor 1 receptor (IGF1R) by competitively adhering to miR-7 to regulate muscle differentiation (40). Two circRNAs generated from the RBFOX2 gene have been involved in chicken myoblast proliferation. They have been reported to enhance myoblast differentiation and proliferation by acting as ceRNA for miR-206 and miR-1a-3p (41,42).

Numerous studies show the role of circRNA in muscle proliferation, differentiation, and muscle diseases. However, the proper mechanism of circRNA functioning is not fully understood yet. Especially the questions related to post-transcriptional regulation of circRNA need to be answered.

1.4 Various circRNAs involved in the myogenesis

1.4.1 CircRBFOX2

A study regarding chicken muscle development found 11 forms of circRNA generated from the parental gene, RBFOX2. The research on the development of chicken's skeletal muscle unveiled the surprising fact that these circRNAs are differentially expressed. CircRBFOX2 possesses binding sites for miR-1a-3p and miR-206 (42). Previous studies determined that miR-206 is the culprit behind the repression of cyclin D2, as cyclin D2 is a much-needed factor required to promote the cell cycle (3). Experiment on the role of circRBFOX2 in chicken muscle development has shown quite interesting results. Overexpression of circRBFOX2 in chicken muscles enhanced muscle proliferation. On the other hand, the same results were seen after knocking down miR-206 in chicken muscles. This experimental verification proposes that circRBFOX2 sponges miR-206, which increases the expression level of cyclin D, ultimately enhancing myoblast proliferation in chicken skeletal muscles (42).

1.4.2 CircSVIL

CircSVIL arises from the exon region of the SVIL gene. circSVIL has been observed to play a constructive role in regulating myogenesis. A recent study on muscle development in chicken has found the involvement of circSVIL in the muscle development of chicken. Plenty of circSVIL is found during the embryonic development of chicken, especially from E10 to E15 and later stages of development. The latest study determined that circSVIL arises from the exon 6-14 region of the supervillain gene on chromosome2 (41). In terms of its role in regulating muscle development, *in silico* analysis showed that circSVIL harbors four adhering sites for miR-203. Ouyang et al. also revealed interaction among circSVIL and miR-203. miR-203 has a negative role in the myogenesis of skeletal muscles by inhibiting the functioning of muscle growth factor c-JUN. While, in the proliferation of myoblasts, c-JUN acts as a helping hand through MAPK/JNK pathway (41). Along with c-JUN, MEF2C (transcription factor) supports muscle differentiation (43). circSVIL sponges miR-203 and helps to enhance both muscle proliferation and differentiation by aggravating the expression level of transcription factors c-JUN and MEF2C.

1.4.3 FGFR2

The role of fibroblast growth factor receptor 2 (FGFR2) in muscle cell proliferation and differentiation is widely known. A recent study by Ouyang et al. reported a circFGFR2 produced from the host gene circFGFR2, which is responsible for muscle development regulation by acting as a miRNA sponge (44). Interestingly, a different expression of circFGFR2 was noted in the skeletal muscle of chicken during embryo formation. Moreover, circFGFR2 has binding sites for both miR-133a-5p and miR-29b-1-5p. Both of these miRNAs are responsible for the suppression of muscle proliferation and differentiation. In short, it can be said that circFGFR2 lessens the role of miR-133a-5p and miR-29b-5p by acting as ceRNA. circFGFR2 enhances the proliferation and differentiation of chicken skeletal muscle (44).

1.4.4 CircLMO7

CircLMO7 originated from the parent gene LMO7, mainly expressed in muscle tissues in bovines. A study indicated the negative regulatory role of circLMO7 in myoblast differentiation by pacing down the expression of MyoD and MyoG. Both factors are believed to be responsible for myoblast differentiation in skeletal muscles. Therefore, circLMO7 inhibits muscle tissue differentiation by sponging the effect of miR-378a-3p. HDAC4 is a factor responsible for increased muscle proliferation (45). HDAC4 is inhibited by miR-378a-3p, enhancing myoblast differentiation in bovine skeletal muscle. CircLMO7 hinders miR-378a3p functioning by adhering to the binding site to reduce apoptosis and enhance myoblast proliferation (46).

1.4.5 CircFUT10

Host gene FUT10 generates circFUT10, which is highly expressed in bovine skeletal muscle, especially during embryonic development. CircFUT10 works by upregulating serum response factor(SRF). Its overexpression induces apoptosis, which fastens muscle differentiation and inhibits muscle proliferation. The study revealed that circFUT10 has three binding sites for miR-133a. MiR-133a plays a crucial role in muscle development by targeting serum response factor (SRF). In short, circFUT10 enhances the expression of SRF, which promotes differentiation and inhibits muscle proliferation by sponging miR-133a (35).

1.4.6 CircFGFR4

CircFGFR4 is highly enriched in the skeletal muscles of bovines. It was determined through RNAhybrid and TargetScan that circFGFR4 has 18 binding sites for miR-107. MiR-107 plays a key part in regulating bovine muscle development by targeting Wnt3a (3,39). Wnt3a is an essential factor, well known for its role in fiber formation in muscles both during prenatal and post-natal phases of myogenic development. MiR-107 reduces apoptosis and myotube formation by inhibiting Wnt3a. In short, circFGFR4 binds to miR-107, induces apoptosis, and promotes muscle differentiation by upregulating Wnt3a (39).

2. Conclusion

To conclude, it is evident that circRNAs are also involved in the regulation of various molecular processes in living organisms. Scientists consider circRNA a new class of noncoding RNAs responsible for regulating skeletal muscle's myogenesis. In recent studies, many CircRNAs has discovered to regulate myoblasts' proliferation and differentiation in various animals including chicken and cattle. Some studies on circRNA have also revealed the role of circRNA in the development of muscular diseases and tumors. Apart from this, circRNA can also be used as a biomarker for different diseases. As skeletal muscle is an essential part of the meat, understanding the proper mechanism about the working of circRNA would prove helpful in the future to meet humanity's food requirements in the future.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there are no competing interests.

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