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REVIEW

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Circular RNA regulation of fat deposition and muscle development in cattle

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Abstract

Circular RNAs (circRNAs) are important transcriptional regulatory RNA molecule that can regulate the transcription of downstream genes by competitive binding of miRNAs or coding proteins or by blocking mRNAs translation. Numerous studies have shown that circRNAs are extensively involved in cell proliferation, differentiation and apoptosis, gene transcription and signal transduction. Fat deposition and muscle development have important effects on beef traits. CircRNAs are involved in regulating bovine fat and muscle cells and are differentially expressed in the tissues composed of these cells, suggesting that circRNAs play an important role in regulating bovine fat formation and muscle development. This review describes differential expression of circRNAs in bovine fat and muscle tissues, research progress in understanding how circRNAs regulate the proliferation and differentiation of bovine fat and muscle cells through competing endogenous RNAs networks, and provide a reference for the subsequent research on the molecular mechanism of circRNAs in regulating fat deposition and muscle development in cattle.

KEYWORDS
cattle, circularRNAs, competing endogenous RNA, fat deposition, muscle development

1 | BACKGROUND

Intramuscular fat (IMF) deposition is an important factor used to determine the quality of meat during beef production and its content directly affects the sensory characteristics and marbling of beef (Twomey et al., 2020). IMF deposition is a complex process involving proliferation, differentiation and maturation of preadipocytes and is regulated by various hormones, enzymes, transcription factors and signalling pathways (Albrecht et al., 2011; Lee et al., 2010). The growth and development of bovine muscle is a long-term and complex process that mainly depends on the proliferation and hypertrophy of muscle fibres, including the formation, proliferation and differentiation of muscle cells and the formation and maturation of muscle tubes and muscle fibres (Buckingham & Vincent, 2009; Sabourin & Rudnicki, 2000; Wigmore & Stickland, 1983). Muscle growth and development involves multiple functional genes that interact with each other to form a complex and precise positive and negative regulatory network (Fatica & Bozzoni, 2014). As upstream regulators of muscle development, paired box family factors 3 and 7 (Pax3 and Pax7) can activate the myogenic determination gene (MyoD) family to promote the proliferation and differentiation of muscle cells (Borycki et al., 1999; McKinnell et al., 2008). Myostatin negatively regulates myocyte development by inhibiting the transcriptional activity of myogenic determinant family members (Taylor et al., 2001). Therefore, the mechanism of fat deposition and muscle development is significant for developing methods for improving meat quality. Moreover, the epigenome comprising

different mechanisms e.g. DNA methylation, remodelling, histone tail modifications, chromatin microRNAs and long non-coding RNAs, interact with environmental factors like nutrition, pathogens, climate to influence the expression profile of genes and the emergence of specific phenotypes (Barazandeh et al., 2019; Masoudzadeh et al., 2020a). Multi-level interactions between the genome, epigenome and environmental factors might occur. Furthermore, numerous lines of evidence suggest the influence of epigenome variation on health and production (Barazandeh et al., 2019; Masoudzadeh et al., 2020b; Moradian et al., 2019). The expression of eukaryotic genes is temporarily and multidimensionally controlled (Mohammadabadi et al., 2021a,b). Only a relatively small set of the entire genome is expressed in each type of tissue, and the expression of genes depends on the stage of development (Tohidi Nezhad et al., 2015). Therefore, gene expression in eukaryotes is specific to each tissue (Shahsavari et al., 2021). Also, the amount of gene products that are made in the same tissue as well as in other tissues that make up that product, regulates the expression of that gene (Mohammadabadi, 2019). One of the basic activities in domestic animals is the study of genes and proteins related to economic traits and their study at the cellular or chromosomal level (Mohamadipoor et al., 2021).

As ubiquitous molecules in mammals, circular RNAs (circRNAs) has high conservatism and stability (Venø et al., 2015). CircRNAs are mostly formed by reverse cyclisation of mRNA exons (Ebbesen et al., 2017) and regulate gene activity at the transcriptional level (Zhang et al., 2013). As molecular sponges of miRNA, circRNAs competitively bind miRNAs in the cytoplasm (Ashwal-Fluss et al., 2014), regulate RNA transcription and affect the splicing of linear homologous genes (Thomas & Sætrom, 2014). CircRNAs also act as a scaffold for protein complex assembly to regulate proteins (Huang & Shan, 2015). RNA–protein interactions encode proteins that regulate lipid metabolism and serve as biomarkers for disease diagnosis and treatment (Jiang et al., 2020; Legnini et al., 2017). CircRNAs contain binding sites for miRNAs, and their sequences are complementary to miRNA 3′ untranslated region (3′ UTR), which may have adsorption relationships and indicate that circRNAs can function as competitive endogenous RNAs (ceRNAs). Some circRNAs have multiple binding sites for a specific miRNA, such as circRS contains more than 70 miR-7 binding sites (Hansen et al., 2013). Other circRNAs contain binding sites of miR-378, miR-34a, miR-145, miR-432 and miR-2400 which are involved in regulating muscle development, either regulating muscle cell proliferation or differentiation (Ebbesen et al., 2017). Therefore, circRNAs regulate cell proliferation, differentiation, and apoptosis through competitive adsorption of miRNAs, thus regulating bovine fat production (Thomas & Sætrom 2014).

We reviewed the differential expression of circRNAs in bovine fat and muscle tissue, regulation of proliferation and differentiation of bovine fat and muscle cells through the ceRNAs mechanism and provided an overview of the molecular mechanism of circRNA regulation in bovine fat deposition and muscle development. The following sections describe the circRNA involved in muscle development of bovine fat production (Table 1).

2 | ADIPOGENESIS AND ITS REGULATORY FACTORS

Adipose tissue is a complex and essential metabolic and endocrine organ that develops primarily from precursor fat cells and stores energy in the form of lipids (Birbrair et al., 2013). Fat cells are derived from mesenchymal stem cells (MSC), which are produced in the mesoderm, and MSC can differentiate into a variety of cell types including adipocytes, myocytes and osteoblasts. No lipid droplets were formed when MSC differentiated into adipocytes. During the proliferative stage, the number of adipose cells increases significantly, and a series of hormones and growth factors are present to promote mitosis. When the number of proliferating adipocytes is too many and exposed to inhibition, the expression of differentiation transcription factors is activated, the cells change from shuttle type to round, and intracellular triglycerides begin to accumulate in large quantities and eventually form lipid droplets. At this point, adipocyte can secrete many cytokines to coordinate and regulate various life activities in animal body, and adipocyte marker genes begin to express in large quantities (Cedikova et al., 2016; Fève, 2005; Gregoire, 2001). Lipid production is a complex and delicate regulatory process, which is regulated by a variety of transcription factors (Figure 1). The signal transduction network mainly consists of PPARγ and C/EBPα, which co-regulate adipocyte differentiation. Such as, PPARγ can be involved in the transcriptional regulation of multiple genes to participate in a variety of cellular functional responses, including adipocyte differentiation, glucose and lipid metabolism, inflammatory response and atherosclerosis. The polymorphism of FABP4 gene mutation sites was significantly correlated with lipid metabolism traits in animals (Hoashi et al., 2008), and its ectopic expression can promote the differentiation of muscle cell derived stem cells (Zhang et al., 2017). C/EBPs are named for their repeated sequence activation of specific gene DNA enhancer CCAAT, which plays an important role in the regulation of adipocyte proliferation and differentiation. Overexpression of C/EBPα promotes adipocyte differentiation, and C/EBPα loses its activation when the binding site of C/EBPα gene sequence changes (Wang et al., 1995).

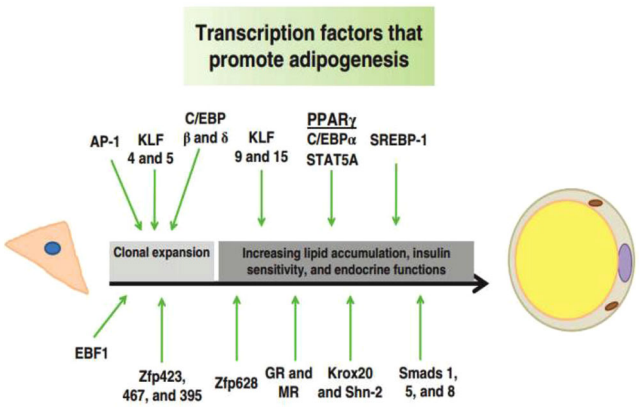

FIGURE 1 Adipogenesis regulators (Mota et al., 2017)

TABLE 1 Summary of circRNAs related to bovine adipogenesis and muscle development

circRNA name	Species	Object	Targeting molecule
circFLT1	Bovine	Adipocyte proliferation and differentiation	miR-93
circFUT10	Bovine	Proliferation, differentiation and apoptosis of adipocytes and myoblasts	Let-7/PPARGC1 miR-133a
circRILPL1	Bovine	Muscle proliferation, differentiation and apoptosis	miR-145/PI3K/AKT
circINSR	Bovine	Proliferation and apoptosis of embryonic muscle cells	miR-34a/Bcl1,CyclinE2
circFGFR4	Bovine	Proliferation and differentiation of myoblasts	miR-107/Wnt3a
circMYL1	Bovine	Proliferation and differentiation of myoblasts	miR-2400
circTTN	Bovine	Proliferation and differentiation of myoblasts	miR-432/IGF2/PI3K/AKT
circMYBPC1	Bovine	Differentiation and regeneration of skeletal muscle	MyHC
circEch1	Bovine/mouse	Myoblast proliferation and differentiation and skeletal muscle regeneration	Unknown
circLMO7	Bovine	Proliferation and differentiation of myoblasts	miR-378a-3p

3 | SKELETAL MUSCLE FUNCTION AND MYOGENESIS

Muscles are an important part of an animal's body (Güller & Russell, 2010). In animal husbandry, skeletal muscle has become an important meat product for human consumption. To a large extent, myogenesis is responsible for the quantity, quality and type of muscle fibres and some muscle-related diseases. Meanwhile, it is also a complex multistage process, during which some signalling pathways may be involved in coordination with some genes. Skeletal muscle cells begin in the embryo's mesoderm and ectoderm and become vertebrae. During embryonic development, some of the somatic cells differentiate into the dermal muscle group, which then divides into muscle group and skin group (Buckingham et al., 2003), Muscle precursor cells (myoblasts) are derived from the myosome and migrate to the limb buds, where they aggregate into back and abdominal muscle masses (Buckingham, 2001). With the migration of myoblasts, specific factors such as Myogenin (MyoG) and Myogenic regulatory factor 4 (Mrf4) were expressed and promoted the fusion of myoblasts into myoducts. Other Myogenic regulatory factors (MRFs) were expressed at the later stage of myoblast proliferation and enhanced myoblast fusion into multinucleated myoducts. When the myotube is first formed, the nucleus is located in the centre of the cell. When the number of myofibrils increases to a certain extent, the nucleus shifts towards the membrane, allowing the myofibrils to form (Stockdale et al., 1997). In addition to the MRFs family of regulatory factors, such as MyoG, myF5, Mrf4 and MyoD, which are involved in the complex process of myogenesis, non-coding regulatory factors have been found to be involved in the regulation of myogenesis, such as miRNAs, lncRNAs and circRNAs.

4 | GENERATION AND FUNCTION OF MIRNAS

MicroRNAs (miRNAs) are a class of endogenous small non-coding RNAs expressed after transcriptional regulation of genes. They are about 22 nt in length and target the 3′UTR region of their target gene, resulting in degradation of mRNA, or some matching of the first 8 bases, inhibiting translation (Krol et al., 2010). There are two approaches to the formation of mature miRNAs: classical and non-classical (Figure 2). There are three main classical molecular mechanisms of miRNAs: guiding miRISC to specifically recognise mRNA and using three post-transcriptional mechanisms to reduce gene expression. (1) Transcriptional inhibition; (2) mRNA degradation and (3) mRNA deglandalisation are universal, and its function is mainly exerted by transcriptional inhibition in animals (Winter et al., 2009; Wu et al., 2006). There are many classical molecular mechanisms of miRNAs, such as pri-miRNA translated into multiple skin; targeting RNA to bind proteins; TLR receptor protein can be activated by miRNA. Upregulated protein expression level, targeted regulation of mitochondrial-related gene mRNA, activating gene transcription and pre-RNA play a negative regulatory role by targeting non-coding RNAs (such as circRNA).

5 | BIOGENESIS AND FUNCTION OF CIRCRNA

Initial studies suggested that the circRNA was generated by the wrong splicing of mRNA, but subsequent studies confirmed that circRNA's production is strictly regulated (Ebbesen et al., 2017). In circRNA reverse splicing, the downstream splic donor site (SD) reverse-binds to the upstream splic acceptor site (SA), so as to form circRNA with no dissociated 3′-ends and 5′-ends and linear RNA with skipped exons (Zhang et al., 2013). Since circRNAs are mostly formed by reverse cyclisation of mRNAs exons, reverse splicing is combined with cis splicing (Ebbesen et al., 2017). Therefore, circRNA generation regulated by reverse splicing mechanism is still influenced by the typical splicing signal and spliceosome mechanism, and its generation is also influenced by some RNA binding proteins and transcription elongation rate (Fischer & Leung, 2017). Most circRNAs are located in the cytoplasm, but some circRNAs are distributed in the nucleus, and the main feature is the ring structure within the molecule, in which the 3′ ends of some

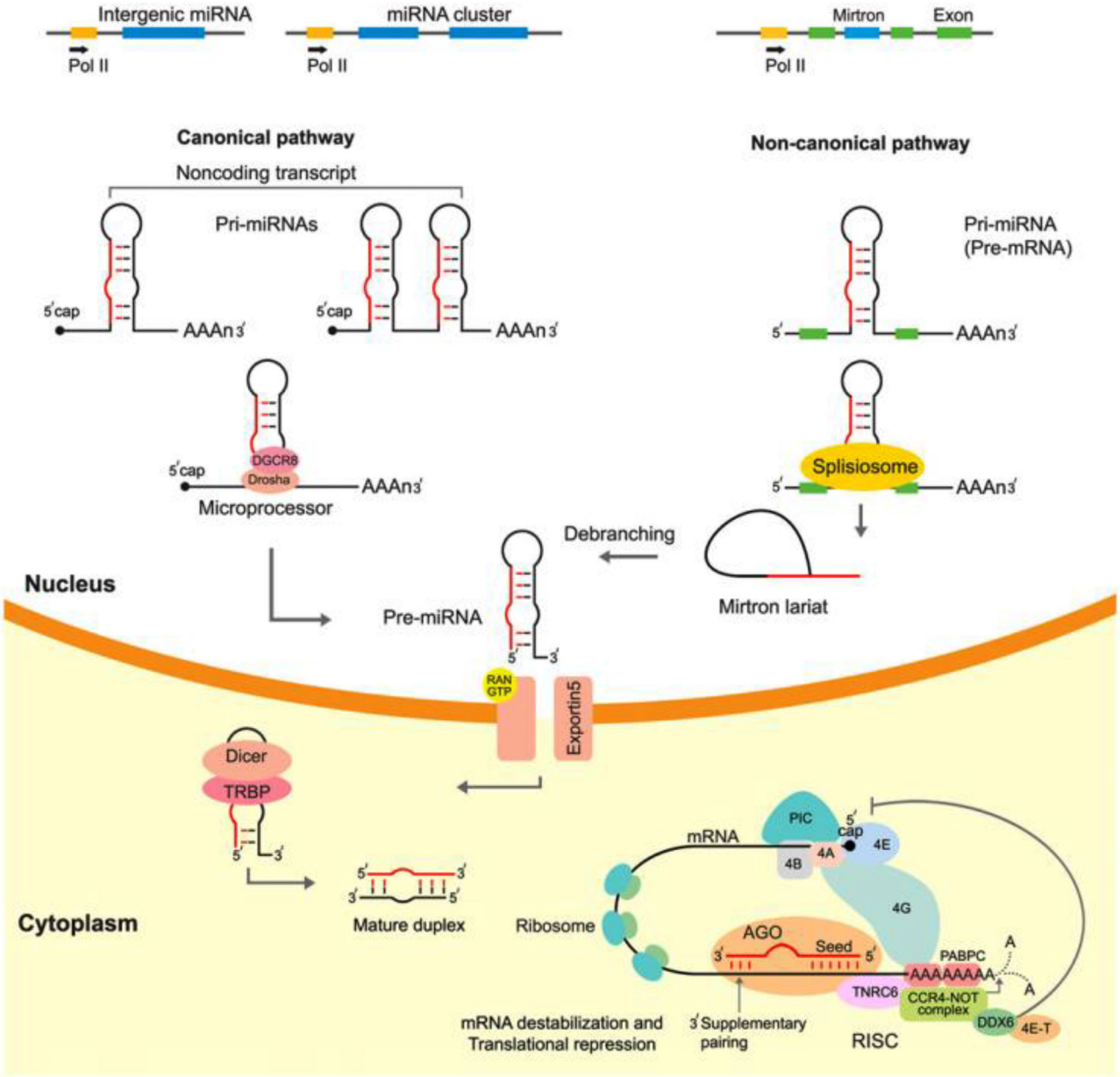

FIGURE 2 Overview of the miRNAs biogenesis (Saliminejad et al., 2019)

exons turn backwards and join with the 5′ ends of other upstream exons to form a closed molecule. Thus, circRNA differs from those typical linear RNAs in that these circRNA transcripts do not have a 5′ cap and 3′ polyadenylate tail. Studies have found that circRNA mainly performs its biological functions in the following ways (Figure 3): regulates gene activity at the transcriptional level (Zhang et al., 2017); as a miRNAs molecular sponge, competitive adsorption of miRNAs (Thomas & Sætrom, 2014); regulates RNA transcription and affects splicing of its linear homologous genes (Ashwal-Fluss et al., 2014); acts as a scaffold for protein complex assembly to regulate proteins (Huang & Shan, 2015); RNA–protein interactions encode proteins that regulate lipid metabolism and serve as biomarkers for disease diagnosis and treatment (Jiang et al., 2020; Legnini et al., 2017).

6 | CIRCRNAS REGULATE FAT DEPOSITION IN CATTLE (FIGURE 4)

6.1 | Screening of differentially expressed circRNAs in bovine adipose tissue

With the development of RNA sequencing (RNA-Seq) and bioinformatics technologies, the relationship between bovine transcriptome-related differential genes and specific traits has been increasingly investigated (Mohammadabadi et al., 2017). CircRNA is different from mRNA, because it has no transcriptional activity and coding ability, so it is often used to study competitive binding molecular sponge and its influence on the gene of origin. Due to its characteristics, circRNA

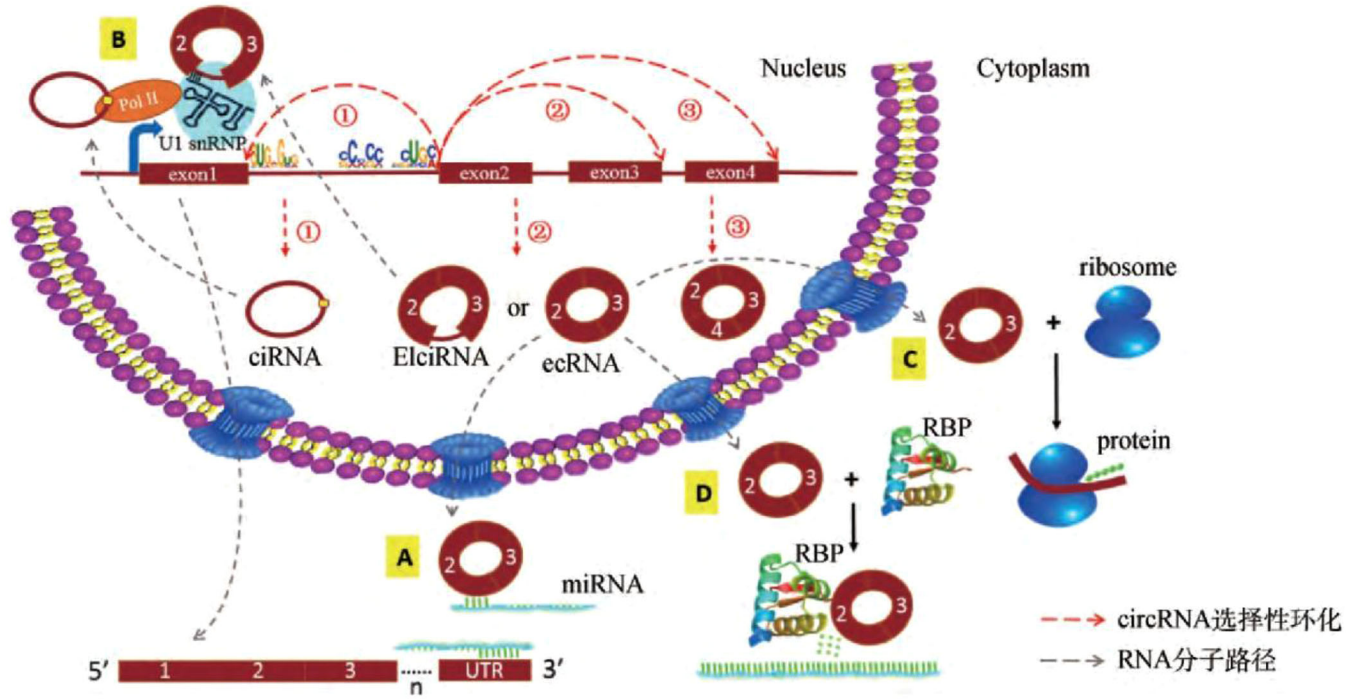

FIGURE 3 The biological function of circRNA (Zhang et al., 2016a,b)

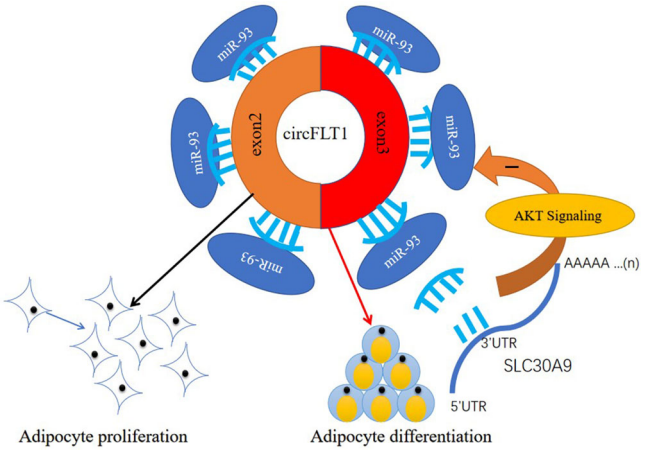

FIGURE 4 CircFLT1 regulates the proliferation and differentiation of adipocytes by sponging miR-93

can be identified on A large scale on RNA-seq (Mohammadabadi et al., 2021a,b). Different from mRNA and lncRNA, circRNA does not contain poly A tail, so circRNA is mainly enriched in RNA without ploy A tail. Poly (A)-RNA-seq technology or RNA-seq technology with linear RNA degraded by RNase R can be used (Lu et al., 2020). Shi et al. (2020) identified 14,649 circRNAs by RNA-Seq and bioinformatics analysis in the intramuscular adipose tissues of Nanyang and Angus cattle, including 75 upregulated and 36 downregulated circRNAs. And they found that the expression levels of circRNA-9560 and circRNA-7431 were significantly decreased and circRNA-2083 and circRNA-6528 were significantly increased by RT-qPCR. Zhang et al. (2020) detected 7203 candidate circRNAs during adipocyte differentiation in yaks, screened 136 differentially expressed circRNAs and constructed a circRNA network related to adipocyte differentiation. Six circRNAs related to adipogenesis were found to be involved in the NF-κB signalling pathway, steroid biosynthesis, glycerol metabolism and cytokine-cytokine receptor interactions. Some differentially expressed circRNAs, miRNAs and genes are co-expressed in the fat and muscle tissues of *Bos grunniens* and are crucial for regulating IMF deposition (Wang et al., 2020). Huang et al. (2019) identified several differentially expressed circRNAs related to buffalo fat deposition by analysing the characteristics of circRNAs in Chinese buffalo adipose tissue; these authors also conducted quantitative PCR analysis and identified numerous circRNAs genes correlated with fat deposition correlation ($|r| > 0.980$). Notably, they identified two potential regulators of fat deposition in buffalo, which are strongly associated with *PRDM16* and may inhibit white fat deposition in buffalo; *PRDM16* activates *PPARγ* to promote adipocyte differentiation (Hallberg et al., 2008). CircRNAs derived from *PPARγ* gene were differentially expressed and highly conserved buffalo adipose tissues and showing potential as candidate genes for fat deposition in cattle (Feng et al., 2019).

6.2 | CircRNAs positively regulate fat deposition in cattle

CircFGFR4 promotes myoblasts differentiation via binding miR-107 to relieve its inhibition of *Wnt3a* (Li et al., 2018). MiR-107 elicits endoplasmic reticulum stress-mediated apoptosis of preadipocytes by targeting the Wnt3a/β-catenin pathway (Ahonen et al., 2019; Zhang

et al., 2018). Therefore, circFGFR4 may promote adipocyte growth via sponge adsorption of miR-107 in bovine preadipocytes. Overexpression of circFLT1 promotes adipocyte differentiation and inhibits proliferation, whereas miR-93 inhibits adipocyte differentiation. CircFLT1 can be used as a ceRNA to adsorb miR-93 eliminate its inhibition of the downstream target gene *SLC30A9* and increase the expression of *SLC30A9*. *SLC30A9* inhibits cell proliferation by inhibiting the activation of the AKT signalling pathway and promotes differentiation by recruiting FOS proteins to the *PPARG* promoter (Kang et al., 2020). However, additional studies are needed to determine whether circFLT1 is associated with other regulatory processes and whether its regulation of adipocyte differentiation is conserved in humans and mice.

6.3 | CircRNAs negatively regulate fat deposition in cattle

CircINSR has been identified as an important regulator of IMF deposition; it can regulate *CyclinE2* and *Bcl-2* genes through miR-34a, significantly promote the proliferation of embryonic myoblasts and reduce cell apoptosis (Shen et al., 2020). MiR-34a inhibits adipose tissue-derived stem cell differentiation by regulating the cell cycles, inducing senescence (Park et al., 2015) and dictating the overexpression of *Bcl-2*, which inhibits adipose cell differentiation. Therefore, it is speculated that inhibiting circINSR expression may promote bovine adipogenesis. Research found that circFUT10 contains binding sites of the Let-7 family, and both circFUT10 and Let-7c can bind AGO2 proteins. The binding of circFUT10 to let-7c promotes cell proliferation and inhibits cell differentiation by targeting *PPARGC1B* in cattle adipocytes. Let-7c inhibited expression of adipogenic markers *PCNA* and *CDK2* and promoted expression of the adipogenic markers *PPARγ* and *C/EBPβ*, which was alleviated by co-expression of circFUT10 (Jiang et al., 2020). *PPARGC1B* can reverse the inhibition of miR-21 on its target gene *CD36* and increase intracellular lipid content (Ni et al., 2019). Thus, during bovine adipose deposition, many circRNAs act as miRNA sponges to regulate the expression of certain genes and control bovine adipose deposition by positively and negatively regulating the proliferation, differentiation and apoptosis of bovine adipose cells, affecting the quality of beef. Although circRNAs have a wide range of biological functions, the relationship between circRNAs and bovine fat deposition is not well understood, and other miRNAs that may be regulated by circRNAs require further analysis.

7 | CIRCRNAS REGULATE BOVINE MUSCLE DEVELOPMENT (FIGURE 5)

7.1 | Screening of differentially expressed circRNAs in bovine muscle tissue

Wei et al. (2017) detected circRNA expression profiles in bovine skeletal muscle at different developmental stages (embryonic and adult longissimus) by RNA-Seq, and they provided the first overview of the types and relative abundance of circRNAs discovered. Many circRNAs were identified, including circular intron RNA, with 74% of circRNAs candidates containing 2–7 exons (Liu et al., 2020a,b). Identified 14,640 circRNAs in muscle of two breeds of cattle (Shandong black and Luxi) and found that 655 circRNAs were differentially expressed. They found that these circRNAs were mainly involved in muscle fibre development; smooth muscle cell proliferation; tight connection of bone system morphogenesis; MAPK, AMPK, mTOR signalling pathways and other biological processes by KEGG and GO analysis. In addition, miRanda predicted interactions between 14 circRNAs and 11 miRNAs. These differentially expressed circRNAs regulate the proliferation and differentiation of bovine muscle cells. A total of 5177 circRNAs were identified in the longissimus dorsi tissue of Kazakh and Xinjiang brown cattle, 46 of which were differentially expressed. Sixty-six interactions were predicted between 65 circRNAs and 14 miRNAs, and a co-expression network was constructed, wherein several miRNAs known to be involved in the regulation of myoblasts such as miR-133b and miR-664a, were found. Notably bta-circ-03789-1 and bta-circ-054533-1 are potential miRNAs sponges or regulating the expression of insulin-like growth factor 1 (IGF1) receptors (Yan et al., 2020). *IGF1* promotes myoblast proliferation and skeletal muscle growth through the PI3K/AKT signalling pathway (Yu et al., 2015). Therefore, bta-circ-03789-1 and bta-circ-054533-1 may regulate the growth and development of bovine muscle cells, but the molecular mechanism of their regulation of bovine muscle development remains unclear.

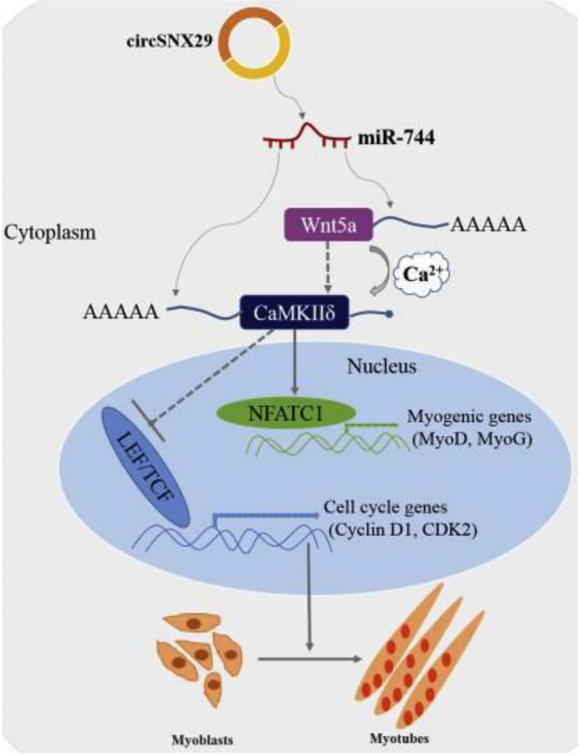

FIGURE 5 Model of the action circSNX29 competitively sponging miR-744 mediating myogenesis (Peng et al., 2019)

7.2 | CircRNAs positively regulate muscle development in cattle

According to sequencing data and bioinformatics analysis, the new circRNA circRIIPL1 acts as a sponge for miR-145 and activates AKT signalling pathway to regulates the *IGF1R* and restores the inhibition of miR-145 on PI3K/AKT signalling pathway (Shen et al., 2021). *IGF1R* has been reported to effectively induce myoblast proliferation and differentiation through the PI3K/AKT pathway (Quinn & Haugk, 1996). Therefore, circRILPL1 is positively correlated with muscle proliferation and differentiation in vitro and can inhibit cell apoptosis, thus promoting the growth of bovine myoblasts. CircMYL1 interacts with miR-2400 to inhibit myoblast proliferation and promote differentiation through the competitive adsorption of miR-2400, which promotes cell proliferation by targeting *MYOG* (Elnour et al., 2021). *MYOG*, a member of the myogenic regulatory factors family, induces terminal differentiation of skeletal muscle (Liu et al., 2020a,b). Therefore, as a circRNA, circMYL1 can activate the *MYOG* gene by sponge-mediated miR-2400 to inhibit the proliferation and promote the differentiation of myoblasts. CircTTN stimulates the proliferation and differentiation of bovine myoblasts by competitively binding with miR-432 to activate the IGF2/PI3K/AKT signalling pathway. MiR-432 inhibited the expression of the *IGF2* gene, but this effect was mitigated by the circTTN (Wang et al., 2019). *IGF2* and *IGF1* also promote myoblast proliferation and skeletal muscle growth through the PI3K/AKT signalling pathway (Yu et al., 2015). CircMYBPC1 binds directly to RNA binding proteins as ceRNA in vitro and induces skeletal muscle regeneration in vivo. CircMYBPC1 alleviates the inhibition of myosin heavy chain (MyHC) by directly binding to miR-23a, which downregulates the expression of *MyHC* by binding to *MyHC* and promotes the differentiation of bovine muscle cells, thus regulating the development of bovine skeletal muscle (Chen et al., 2021). Therefore, the absorption of miR-23a by circMYBPC1 sponge regulates MyHC gene and positively regulates muscle development in cattle.

7.3 | CircRNAs negatively regulate muscle development in cattle

CircINSR promotes the proliferation of bovine myoblasts by adsorption of miR-34A and the development of bovine embryonic muscle by targeting miR-34a. CircINSR contains two target sites of miR-34a, miR-34a inhibits the proliferation of bovine muscle cells and promotes apoptosis. However, co-transfection of circINSR with miR-34a reversed this effect. In addition, the expression of the miR-34a target genes *Bcl-2* and *cyclin-2* are regulated by circINSR, demonstrating that circINSR can act as a sponge for miR-34a at the molecular and cellular levels and function by inhibiting target genes in muscle cells (Shen et al., 2020). CircEch1 is one of the most upregulated circRNAs during muscle development and is an important regulator of bovine myoblasts differentiation and skeletal muscle regeneration to regulate the development of bovine skeletal muscle in vitro and induce skeletal muscle regeneration in vivo. CircEch1 overexpression promotes the proliferation of bovine myoblasts and inhibits their differentiation. Therefore, circEch1 shows potential as a target for promoting muscle development and myogenesis (Huang et al., 2021). CircHUWE1 relieved AKT3 inhibition of cell differentiation by directly interfering with miR-29b to promote the proliferation of bovine myoblasts and inhibit cell differentiation and apoptosis (Yue et al., 2020). MiR-29b positively regulates adipogenic differentiation by enhancing sp1-mediated TNF-α inhibition (Zhang et al., 2016a,b). CircLMO7 is among the most downregulated circRNAs between adult and embryonic muscle tissues during bovine muscle development and is a ceRNA of miR-378a-3p. CircLMO7 inhibits *MyoD* expression via the spongy adsorption of miR-378a-3p. CircLMO7 can promote the proliferation and inhibit the differentiation of bovine muscle cells. The involvement of miR-378a-3p in bovine muscle development has been previously reported; and the overexpression of miR-378a-3p promotes the expression of *MyoD*, a myoblast determinant, and induces myotube forming. This effect was not observed after the overexpression of circLMO7, which promotes the proliferation of myoblasts, prevents apoptosis, and may significantly reduce the expression of mature markers *MyoD* and *MyoG* generated by the bovine muscle. CircLMO7 increases the number of myoblasts in the cell cycle S phase and decreases the proportion of cells in G0/G1 phase. Overexpression of miR-378A-3p increases the number of G0/G1 phase myoblasts (Wei et al., 2017). Therefore, inhibiting circLMO7 expression can promote muscle development in cattle.

In conclusion, circRNAs differentially expressed in different bovine muscle tissues can regulate fat deposition and muscle development in cattle. CircRNAs regulate the proliferation and differentiation of bovine fat and muscle cells through ceRNA mechanisms and are important role in regulating fat deposition along with muscle growth and development. These results provide a basis for an in-depth analysis of the role of circRNAs in adipogenesis, myogenesis and muscle diseases. Furthermore, the results provide important information on the regulation of circRNAs in fat deposition and muscle development of different breeds of cattle and materials for future researchers to explore the molecular mechanism of circRNAs in these processes. Further studies are needed to identify the inducers of differential expression of circRNAs isoforms of a parent gene and whether different circRNA isoforms have different functions.

8 | SUMMARISATION AND OUTLOOK

The formation of bovine fat and muscle tissue involves complex developmental and physiological processes and plays a crucial role in determining beef quality. CircRNAs, as transcriptional regulatory factors, can regulate the proliferation and differentiation of bovine adipocytes and muscle cells; affect fat deposition and muscle development of cattle and ultimately affect the beef's taste, tenderness and some meat-related traits. Functional studies of circRNAs involved in regulating fat and muscle cells have attracted extensive research attention. Studies have identified several circRNAs that may play important roles in cattle fat deposition and muscle development. However, current studies

are limited to functional annotations, expression verification and the construction of circRNA-miRNA-mRNA endogenous competitive networks of identified circRNAs. There are few reports on the molecular mechanism of circRNA regulating fat deposition and muscle development in cattle. At present, circRNA has been explored as part of ceRNA pathways. Further studies are needed for regulatory network and functional verification involving circRNAs and identifying more circRNAs involved in regulating bovine fat deposition and muscle development. These studies improve the understanding of the formation and biological function of circRNAs and other regulatory networks related to bovine fat deposition and muscle development.

LncRNAs can also adsorb miRNAs as molecular sponges, but due to the existence of antisense lncRNAs, they are more suitable than circRNAs for studying source genes. MiRNAs generally exist as 'intermediaries' in competitive binding networks. What genes can they target that represent the function of upstream lncRNAs and circRNAs. However, as we know, miRNAs are conserved among species and their sequences are consistent, but the gene sequences of different species may not be completely consistent, which also leads to different genes targeted by miRNAs, which also leads to a variety of possibilities for our research.

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CONFLICT OF INTEREST

There is no conflict of interest in this manuscript, and the manuscript is approved by all authors for publication.

AUTHOR CONTRIBUTIONS

GYH wrote and revised the manuscript and was a major contributor in writing the manuscript; MYF, WSZ and LZX helped revise the manuscript; MY was the project leader, guiding the manuscript writing and revision. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

PEER REVIEW

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