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The emerging roles of circular RNAs in regulating the fate of stem cells

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Abstract
Circular RNAs(circRNAs) are a large family of RNAs shaping covalently closed ring-like molecules and have become a hotspot with thousands of newly published studies. Stem cells are undifferentiated cells and have great potential in medical treatment due to their self-renewal ability and differentiation capacity. Abundant researches have unveiled that circRNAs have unique expression profile during the differentiation of stem cells and could serve as promising biomarkers of these cells. There are key circRNAs relevant to the differentiation, proliferation, and apoptosis of stem cells with certain mechanisms such as sponging miRNAs, interacting with proteins, and interfering mRNA translation. Moreover, several circRNAs have joined in the interplay between stem cells and lymphocytes. Our review will shed lights on the emerging roles of circRNAs in regulating the fate of diverse stem cells.

Keywords Circular RNA · Stem cells · Cell differentiation · Cell proliferation · Apoptosis

Introduction

Circular RNAs(circRNAs) are a large class of non-coding RNAs forming covalently closed loop structures with neither 5′–3′ polarities nor polyadenylated tails, which are different from linear RNAs. CircRNAs are more stable than linear RNAs as a result of their ring structures protecting them from exonuclease-mediated degradation [1]. Unlike canonical linear splicing, circRNAs are produced from precursor mRNAs (pre-mRNAs) by a non-canonical splicing event called backsplicing in which a downstream splice-donor site is covalently linked to an upstream splice-acceptor site, thus forming a ring structure. The first report of circRNAs was published in 1976 by Sanger et al., who found viroids to be covalently closed circular RNA molecules [2]. However, circRNAs were regarded as experimental artifacts or accidental splicing by-products at that time [3]. Development of RNA deep sequencing and ribosomal RNA depletion technology made it possible to take a deeper look at circRNAs and a surprising work declared circRNAs to be extensive in human genes [4]. In 2013, two articles were posted simultaneously in Nature which discovered two circRNAs to be microRNA(miRNA) sponges: antisense to the cerebellar degeneration-related protein 1 transcript (CDR1as) and circular sex-determining region Y (circSry), unveiling functions of circRNAs for the first time [5, 6]. Plenty of researches have emerged ever since and circRNAs are now found to be widespread, diverse, conserved, and cell type specific [7–9].

The detailed mechanisms for circRNA biogenesis have not been completely illuminated. There are several dominating models about circRNAs biogenesis. Jeck et al. proposed two models about circRNAs biogenesis. One was termed "lariat-driven circularization" which assumed that lariat formation during exon skipping, an event splicing alternative exons out of the final mRNA product as a lariat, triggered circularization. The other one was "intron-pairing-driven circularization" which indicated that base pairing between inverted repeat elements initiated circularization via bringing a downstream splice-donor site into proximity with an upstream splice-acceptor site [7]. Liang et al. also added evidence to this model by demonstrating that the miniature introns containing splice sites and short (30–40 nt) inverted

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repeats were sufficient for circRNAs formation [10]. Besides from intron pairing, RNA binding proteins (RBPs) were also able to mediate looping formation [11, 12]. Moreover, RNA-editing enzyme ADAR1 suppressed the biogenesis of circRNAs by Adenosine-to-Inosine (A-to-I) editing which could diminish RNA pairing structure of flanking introns and decrease backsplicing efficiency [13]. CircRNAs are discovered to have important biological functions [14], but most of which have been miRNA sponges [5, 6]. CircRNAs located in cytoplasm contain complementary miRNA binding sites and could bind to miRNA and inhibit their effects on target mRNAs, which is termed "miRNA sponge". CircRNAs could also bind to proteins and suppress their functions [15, 16]. In the nucleus, circRNAs could regulate parental gene transcription [17] and regulate alternative splicing [18, 19]. In addition, circRNAs were considered to be unable to translate for a long time. However, researchers found that circRNAs could translate into proteins or peptides [20–23]. Further studies are necessary to clarify other potential functions of circRNAs.

Stem cells are immature cells talented to immortalize themselves via self-renewal and to produce mature cells of one or several specific tissues through differentiation [24]. Long non-coding RNAs (LncRNAs) have been confirmed to be involved in the differentiation of stem cells in many studies [25]. Similar tolncRNAs, circRNAs also belong to competing endogenous RNAs and accumulating evidence has suggested that they may participate in regulating growth and differentiation of various types of stem cells and in the retrieval of stemness [9, 11, 20]. This review will concentrate on the emerging roles of circRNAs in intervening in the fate of stem cells.

CircRNAs' general characteristics in the differentiation of stem cells

CircRNAs exhibit unique expression patterns in the differentiation of stem cells

CircRNAs were exposed to be conserved from human to simple organisms, for instance, fungi [6, 7, 26]. Likewise, the profile of circRNAs in the differentiation of stem cells was also revealed to be conserved. CircRNAs were conserved in myoblasts and myotubes between human and mouse with overlap being 40% [20]. Genes from which circRNAs arose during the differentiation of hematopoietic stem cells (HSCs) were enriched in housekeeping functions [27]. During the differentiation and β-adrenergic stimulation of human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), circRNAs were conserved between human, mouse, and rat and four homologs: circMYOD, circSLC8A1, circATXN7, and circPHF21A were revealed to associate with ribosomes and/or AGO2 protein complexes, signifying a potential role for these circRNAs in the regulation of RNA translation [28].

Numerous research papers have pointed out that circRNAs are differentially expressed, mostly upregulated (Table 1) and derived from exonic regions in the differentiation of stem cells [29–32]. Nevertheless, thousands of novel intronic circRNAs were noticed in mouse myoblasts far more than exonic circRNAs via a novel high-purity circular RNA isolation method (RPAD), questioning whether the result of most aberrantly expressed circRNAs coming from exons was due to inexact methods [33]. Upregulation of circRNAs was in line with preceding studies and often treated as a result of their stability and regulation of trans-acting factors, such as ADAR1, DHX9, and muscleblind (MBL) [20, 34, 35]. During the differentiation of human embryonic stem cells(hESCs) towards 3D-laminated retina, MBL was found to be upregulated as circularization promotor, ADAR1,and DHX9 were downregulated as circularization inhibitor and circRNAs were increased [32]. This study also found that circRNAs produced from non-coding genes accounted for a higher percentage of transcriptions from their host genes than circRNAs from coding genes. The top two non-coding circRNAs: circRMST and circFIRRE were found to be the dominant isoforms of their original loci which were proved to involve in developmental processes [32, 36, 37]. Apart from trans-acting factors, Xie et al. speculated that certain lengths might prefer circularizing[30]due to their examination of differentially expressed circRNAs lengths in subventricular zone (SVZ, recognized as stem cells niche in the brain of mature mammals) compared to cortex. They found that most exonic circRNAs (82.2%) were shorter than 1000nt, with the average length being 537nt. Notable increases were also observed in the genomic span of circRNAs during the differentiation of hESCs [32].

It might be assumed that the expression level of circRNAs is relevant to their host gene expression. Nevertheless, many articles discovered that expression of some circRNAs was independent of expression of their host genes [28, 46, 50, 51], which meant some circRNAs and the linear RNA products of their host gene did not change simultaneously. This indicated that circRNAs not only were by-products of mRNA splicing, but also regulated products of alternative splicing, putting on an additional layer to the complicacy of genetic expression. Kristensen et al. found that circRNAs were overall increased during the differentiation of epidermal stem cells (EpSCs). DNA methylation did not regulate the aberrantly expressed circRNAs directly since no overlap was found between the upregulated circRNAs upon differentiation and upon knockdown of DNMT3A or DNMT3B. They also found upregulated circRNAs had more AGO2 and miRNA binding sites and less Alu-mediated biogenesis than stably

Table 1 CircRNAs' profile during the differentiation of stem cells

Differentiation		Methods	Cells	Species	Results	References
Mesodermal	Osteogenesis	Microarray	BMSCs	Homo sapiens	3938 upregulated and 1505 downregulated	[38]
		Microarray	ADSCS	Homo sapiens	171 upregulated and 119 downregulated	[39]
		Microarray	MSMSCs	Homo sapiens	32 upregulated and 18 downregulated	[40]
		High-throughput sequencing	PDLSCs	Homo sapiens	766 upregulated and 690 downregulated	[41]
		High-throughput sequencing	PDLSCs	Homo sapiens	Changed in a temporal manner	[42]
		High-throughput sequencing	DFCs	Rattus norvegicus	138 upregulated and 128 downregulated	[43]
		High-throughput sequencing	MC3T3-E1 cells	Mus musculus	74 upregulated and 84 downregulated	[31]
		Microarray	ADSCs	Mus musculus	Changed in a temporal manner	[44]
		Microarray	MC3T3-E1 cells	Mus musculus	14 upregulated and 44 downregulated	[45]
	Myogenesis	Microarray	Myoblasts	Homo sapiens	Overall increased	[20]
	Cardiogenesis	High-throughput sequencing	IPSCs	Homo sapiens	Overall increased	[46]
		High-throughput sequencing	IPSCs	Homo sapiens	251 differentially expressed	[28]
		Microarray	IPSCs	Homo sapiens	127 upregulated and 99 downregulated	[47]
	Hematopoiesis	SRA repository from NCBI	HSCs	Homo sapiens	Overall increased	[27]
		Microarray	HSCs	Mus musculus	107 upregulated and 49 downregulated	[48]
Ectodermal	Neurogenesis	High-throughput sequencing	NSCs	Rattus norvegicus	471 upregulated and 508 downregulated	[30]
		High-throughput sequencing	NSCs	Mus musculus	Changed in a temporal manner	[49]
	Retinogenesis	High-throughput sequencing	ESCs	Homo sapiens	Increased from day45 to day0 and stable from day90 to day45	[32]
	Keratogenesis	High-throughput sequencing	EpSCs	Homo sapiens	Overall increased	[50]

BMSCs bone marrow stem cell, *ADSCs* adipose-derived stromal cells, *MSMSCs* maxillary sinus membrane stem cells, *PDLSCs* periodontal ligament stem cells, *DFCs* dental follicle cells, *IPSCs* induced pluripotent stem cells, *NSCs* neural stem cells, *ESCs* embryonic stem cells, *EpSCs* epidermal stem cells, *HSCs* hematopoietic stem cells

expressed circRNAs [50]. The former suggested that differentiated cells were less apt to miRNA regulation with stronger effects of circRNA decoy, while the latter coincided with the upregulation of DHX9 in the differentiated cells. DHX9 was confirmed to weaken the expression of circRNAs with flanking reverse complementary Alu repeats [52]. The authors came up with an assumption that cells positively attenuated the expression of some useless or undesirable circRNAs via upregulating DHX9 [50] There are also some studies about circRNAs' profile in stem cells involved in diseases or under specific conditions (Table 2), exposing the underlying effects of circRNAs on stem cells against internal or external changes and on stem cells repairing damaged tissue.

CircRNAs may serve as promising biomarkers for distinguishing stem cells

CircRNAs have longer half-lives than corresponding linear RNAs on account of their greater resistance to RNA exonucleases. Being secreted extracellularly with high stability and prevalence makes circRNAs promising biomarkers [56]. Numerous articles have reported circRNAs as potential molecular markers for cancer [57, 58]. But only few uncovered the potency of circRNAs as biomarkers for distinguishing stem cells or specific cell lines differentiated from stem cells. CircFOXP1 came from the FOXP1 gene and was verified as a marker of mesenchymal stem cells (MSCs) undergoing strict examination. Firstly, it was

Table 2 CircRNAs' profile in stem cells involved in diseases or under specific conditions

Methods	Cells	Species	Conditions	Results	References
High-throughput sequencing	BMSCs	Rattus norvegicus	Silence of estrogen receptorβ	78 upregulated and 68 downregulated	[53]
Microarray	WJ-MSCs	Homo sapiens	Coculture with damaged endometrial stromal cells	5423 upregulated and 2334 downregulated	[54]
High-throughput sequencing	PDLSCs	Homo sapiens	Mechanical force	1191 upregulated and 1487 downregulated	[29]
High-throughput sequencing	sMSCs	Homo sapiens	Normal skin and Psoriatic lesion	123 upregulated and 6 downregulated	[55]

BMSCs bone marrow stem cell, *WJ- MSCs* Wharton's jelly-derived MSCs, *PDLSCs* periodontal ligament stem cells, *sMSCs* skin mesenchymal stem cells

validated as the strongest downregulated circRNA in all differentiated mesodermal cell types compared with MSCs. Then, here came the same results in primary human tissues. Thirdly, a time course analysis confirmed the degradation of circFOXP1 during MSCs differentiation. Finally, samples originating from different sources(cord blood, bone marrow, adipose tissue and Wharton's jelly) and from male and female donors demonstrated that circFOXP1 expression connected with cell sources and gender, indicating this circRNA could be a specific biomarker of undifferentiated MSCs [59].

HiPSC-CMs produced by present methods are not prepared for clinical use as those cells are heterogeneous groups containing non-CM cells. Scientists eagerly search for reliable circRNA biomarkers in cardiac differentiation for screening hiPSC-CMs. Lei et al. produced hiPSCs from fibroblasts and then differentiated hiPSCs into CMs. Results revealed that circALPK2, circCACNA1D, circSLC8A1 and circSPHKAP were abundant in hiPSC-CMs and particularly ample in fetal heart instead of other tissues (brain, spine, liver and stomach), which meant they were cardiac specific [46]. Those four circRNAs were also validated to increase in the differentiation of hESC towards CMs and circSLC8A1-1 was proved to be the most abundant cardiac-expressed circRNA [51]. These circRNAs hold promising potential to be biomarkers of cardiomyocytes. Xie et al. discovered 41 uniquely expressed circRNAs in adult rat SVZ and believed that they could become biomarkers of mature neural stem cells due to their tissue specificity. Compared to the two well-designed trials above, this speculation obviously needed more extensive investigation [30].

Key circRNAs in stem cells

We summarized key circRNAs involved in regulating stemness and pluripotency of stem cells, and in the differentiation, proliferation, and apoptosis of stem cells. We also referred to two circRNAs involved in the 'cross-talk' between stem cells and lymphocyte. These circRNAs play pivotal roles in stem cells (Fig. 1).

CircRNAs regulate stemness and pluripotency of stem cells

CircBIRC6

CircBIRC6 originated from gene BIRC6 locating on human chromosome 2. Yu et al. found that circBIRC6 promoted pluripotency of hESCs by binding to miR-34a and miR-145 [60]. MiR-34a and miR-145 were demonstrated to attenuate the function of pluripotency-associated genes: NANOG, OCT4, and SOX2 [61]. CircBIRC6 could relieve the suppression of abovementioned target genes as a miRNA sponge. The experimental results also showed that NANOG and OCT4 upregulated the level of one splicing factor (SF): epithelial-splicing regulatory protein 1 (ESRP1). ESRP1 facilitated the biogenesis of circBIRC6 in hESCs. Therefore, a molecular circuitry of circBIRC6 regulating hESCs pluripotency was formed. This research also showed that disturbance of ESRP1 lowered the level of NANOG and OCT4, indicating a possibility that ESRP1 directly regulated OCT4 and NANOG to reinforce pluripotency. ESRP1 and OCT4/NANOG might form a positive feedback as they mutually modulated the expression and effects of themselves and circRNAs, thus maintaining the pluripotency in hESCs (Fig. 2). CircCORO1C was proved to influence the pluripotency of hESCs, too. However, it was discovered not likely to act as a miRNA sponge or mRNA competitor and the authors surmised that it might work through interacting with proteins [60].

Although circBIRC6 and circCORO1C were considered to intervene pluripotency, the expression of circBIRC6 or circCORO1C alone was insufficient to reprogram human fibroblasts into iPSCs. However, co-expressing circBIRC6 or circCORO1C with OCT4,

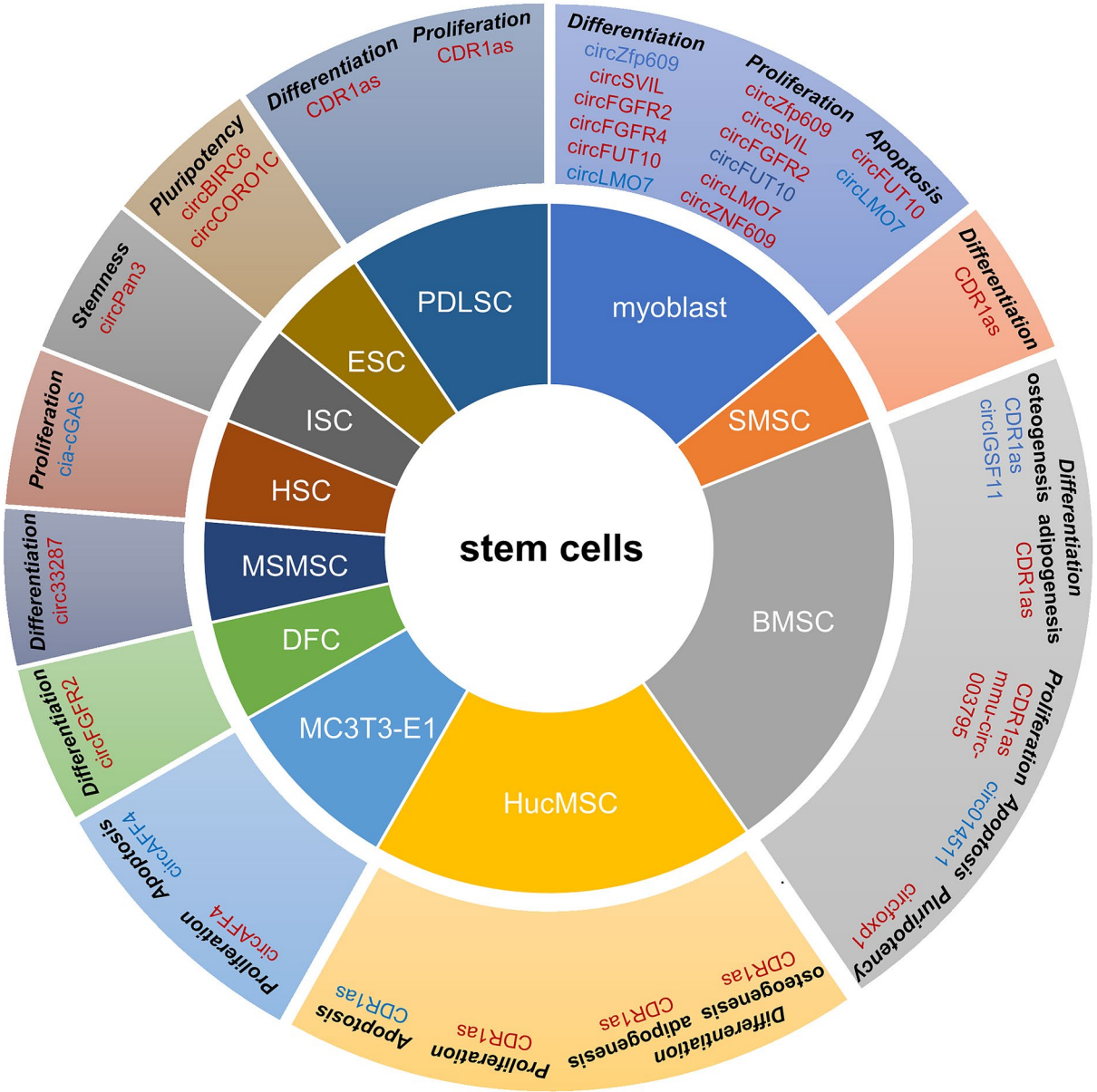

Fig. 1 Key circRNAs in stem cells. Key circRNAs involved in the pluripotency and stemness, proliferation, differentiation, and apoptosis of stem cells are classified according to different kinds of stem cells: embryonic stem cells and adult stem cells from different organs. CircRNAs' functions are marked in different colors. Red fonts: promoting or retaining; Blue fonts: inhibiting. *ESC* embryonic stem cell, *SMSC* skeletal muscle satellite cell, *BMSC* bone mesenchymal stem cell, *HucMSC* mesenchymal stem cell derived from human umbilical cord, *PDLSC* periodontal ligament stem cell, *DFC* dental follicle cell, *MSMSC* maxillary sinus membrane stem cell, *HSC* hematopoietic stem cell, *ISC* intestinal stem cell

SOX2, KLF4, and c-MYC (OSKM) in human fibroblasts potentiated iPSCs formation. Perhaps the reason lay in that circBIRC6 or circCORO1C alone was not enough to initiate all pathways and combination with conventional factors OSKM made reprogramming more effective [62].

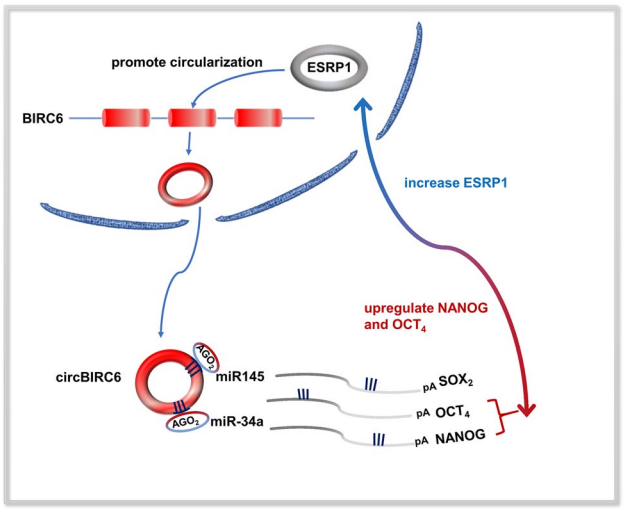

Fig. 2 The molecular circuity of circBIRC6 regulating the pluripotency of hESC. CircBIRC6 could sponge miR-34a and miR-145 and relieved the suppression of their target genes: NANOG, OCT4, and SOX2. NANOG and OCT4 were found to upregulate ESRP1, which facilitated the biogenesis of circBIRC6. ESRP1 was also discovered to regulate NANOG and OCT4. *ESRP1* epithelial-splicing regulatory protein 1, *AGO2* Argonaute2, *hESC* human embryonic stem cell

CircFOXP1

CircFOXP1 was derived from the FOXP1 gene spanning five exons and was flanked by introns containing many Alu repeats on both sides. Its parental gene FoxP1 was found to mediate stabilization of β-catenin, while translocation of stabilized β -catenin to nucleus promoted the maintenance of intestinal stem cells(ISCs) [63] Alessandro et al. studied the biogenesis, functions and mechanisms of circFOXP1 in MSCs [59]. This study unveiled the pivotal role of circFOXP1in maintaining the pluripotency of MSCs through binding to miR-17–3p and miR-127–5p, resulting in upregulating their target mRNAs of non-canonical Wnt and EGFR pathways. Activation of those two signaling pathways were essential to MSCs as sustaining its multipotency and regenerative capacity [64, 65]. MSCs was reprogrammed into hiPSCs and circFOXP1 was downregulated during the process which allowed miR-17-3p/miR-127-5p-mediated inhibition of non-canonical Wnt pathway and reinforced the canonical Wnt pathway. CircFOXP1 was upregulated through the process of hiPSCs generating MSCs and an opposite effect on canonical and non-canonical Wnt signaling was observed [59].

Key circRNAs involve in the differentiation of stem cells

Stem cells are expected to differentiate into specific cell lineages and repair or replace corresponding tissues in clinical treatment. So, it is very important to understand the underlying mechanisms of stem cells differentiation. Here, we summarized key circRNAs involved in the differentiation of stem cells (Table 3).

CircZfp609

CircZNF609 was proved to be highly conserved between mouse and human genome. It also could translate into protein in human myoblasts [20]. CircZfp609 was murine ortholog of circZNF609. Wang et al. showed that circZfp609

Table 3 Key circRNAs involved in the differentiation of stem cells

Cell type	Species	CircRNA	Function	Mechanism	References
Myoblasts	Mus musculus	CircZfp609	Inhibit myogenesis	Sponge miR-194-5p	[66]
	Gallus gallus	CircSVIL	Promote myogenesis	Sponge miR-203	[67]
		CircFGFR2	Promote myogenesis	Sponge miR-133a-5p and miR-29b-1-5p	[68]
	Bos taurus	CircFGFR4	Promote myogenesis	Sponge miR-107	[69]
		CircFUT10	Promote myogenesis	Sponge miR-133a	[70]
		CircLMO7	Inhibit myogenesis	Sponge miR-378a-3p	[71]
DFCs	Rattus norvegicus	CircFGFR2	Promote osteogenesis	Sponge miR-133	[68]
PDLSCs	Homo sapiens	CDR1as	Promote osteogenesis	Sponge miR-7	[72]
HucMSCs	Homo sapiens	CDR1as	Promote adipogenesis and osteogenesis	Unknown	[73]
SONFH-BMSCs	Homo sapiens	CDR1as	Promote adipogenesis and inhibit osteogenesis	Sponge miR-7-5p	[74]
SMSCs	Homo sapiens	CDR1as	Promote myogenesis	Sponge miR-7	[75]
MSMSCs	Homo sapiens	Hsa-circ33287	Promoted osteogenesis	Sponge miR-214-3p	[40]
BMSCs	Homo sapiens	CircIGSF11	Inhibit osteogenesis	Sponge miR-199b-5p	[38]

DFCs dental follicle cells, *PDLSCs* periodontal ligament stem cells, *HucMSCs* mesenchymal stem cells derived from human umbilical cord, *SONFH-BMSCs* bone marrow mesenchymal stem cells from patients with steroid-induced osteonecrosis of the femoral head, *BMSCs* bone marrow stem cells, *SMSCs* skeletal muscle satellite cells, *MSMSCs* maxillary sinus membrane stem cells

could bind to miR-194-5p and sequester its impairment on BCLAF1(BCL-2-associated transcription factor1), so as to repress the myogenic differentiation [66]. Similarly, former study discovered that the balance between miR-194-5p and its newfound target gene BCLAF1 regulated differentiation and survival of hematopoietic progenitors [76].

CircSVIL and CircFGFR2

CircSVIL located on the reverse strand of chromosome 2(Gallus, region:14597995-14657468) and was generated by exon 6 to 14 of SVIL (ENSGALT00000011863.4). It was confirmed that circSVIL enhanced target genes of miR-203(c-JUN and MEF2C) as a miRNA sponge, and exerted a positive effect on chicken myogenesis [67]. Previous study verified miR-203 could suppress differentiation of muscle cells by decreasing the level of c-JUN and MEF2C, which were proved to be significant for myogenesis via loss-and-gain function analyses [77]. CircFGFR2 also influenced chicken myogenesis. It derived from exon 3–6 of fibroblast growth factor receptor2 (FGFR2) gene and was differentially expressed during the development of chicken embryonic skeletal muscle. CircFGFR2 was proved to promote chicken myoblasts differentiation as sponge of miR-133a-5p and miR-29b-1-5p, which were disclosed to inhibit chicken primary myoblasts differentiation [68]. These two miRNAs belonged to RNA families: miR-133 and miR-29, respectively. However, the two families were described to facilitate mouse myoblasts differentiation, opposite to the results in this study [78, 79]. Moreover, with its location on chr1:200648164-200658087 in rat dental follicle cells (DFCs), loss-and-gain function trials verified the enhancement of circFGFR2 on osteogenesis of rat DFCs through targeting miR-133 and relieving its effects on BMP6. BMP6 was reported previously to increase the osteogenic differentiation [80].

CircFGFR4, circFUT10 and CircLMO7

CircFGFR4, circFUT10 and circLMO7 took part in the bovine myogenesis. CircFGFR4, with its host gene FGFR4 locating on chromosome7, was 963 nucleotides long. MiR-107 was plentiful in bovine muscle tissue and could be decoyed by circFGFR4. In other words, circFGFR4 could bind to miR-107, sequester it and inhibit its biological function, which is also called circRNAs' sponge function. CircFGFR4 elevated the level of wnt3a as target gene of miR-107 and promoted myoblasts differentiation [69]. CircFUT10 got name from its host gene FUT10 locating on chromosome 27. It could act as a sponge to relieve the inhibiting effects of miR-133a on serum response factor (SRF), which was essential for muscle growth. [70, 81]. CircLMO7 was the most downregulated circRNA between embryonic and adult bovine skeletal muscles, which located on chromosome12. Overexpressing circLMO7 and miR-378a-3p through vectors and mimics verified that it suppressed myoblasts differentiation and acted as a ceRNA sponging miR-378a-3p, mitigating the inhibition effects of miR-378a-3p on HDAC4 [71], which had been illustrated to intervene in bovine muscle development previously [82].

CDR1as

CDR1as was reported to have more than 60 conserved miR-7 binding sites and function as an miR-7 sponge [5, 6]. As a well-studied circRNA, CDR1as was confirmed to have many biological functions such as influencing transcription and secretion of insulin [83], affecting brain function [84, 85] and regulating melanoma development [86]. Our study found that CDR1as expressed differentially in the osteogenesis of PDLSCs [42].CDR1as could act as a miR-7 sponge, trigger the upregulation of GDF5 and initiate the pSmad1/5/8 and p-p38 MAPK pathway, thus promoting osteogenic differentiation of PDLSCs [72].

CDR1as was abundant in mesenchymal stem cells derived from human umbilical cord (hucMSCs). CDR1as knockdown impaired the ability of hucMSCs to differentiate into adipocytes or osteocytes and downregulated the expression of stemness transcription factors [73]. The regulatory mechanism needed more in-depth study. CDR1as was also found to play critical roles in myogenesis as promoting myogenesis of skeletal muscle satellite cells. Overexpression or knockdown of CDR1as significantly induced or impaired muscle differentiation, respectively. By competitively binding to miR-7, CDR1as relieved its downregulation of IGF1R (insulin like growth factor 1 receptor),which activated myogenesis [87]. Moreover, this study also found MyoD (myogenic differentiation protein 1), a driven transcription factor for myogenesis [88], promoted transcription of CDR1as by binding on its 5′ flank region.[75].

Contrary to the above three, CDR1as inhibited the osteogenesis and promoted adipogenesis of bone marrow mesenchymal stem cells from patients with steroid-induced osteonecrosis of the femoral head (SONFH-BMSCs). CDR1as could bind to miR-7-5p, increase WNT5B expression and inhibit β-catenin [74]. low-expression β-catenin could promote the expression of peroxisome proliferator-activated receptor (PPARγ), thereby promoting adipogenesis of BMSCs [89]and inhibiting osteogenesis of MC3T3-E1 cells [90]. This study provided a better understanding of the molecular mechanism of osteogenesis/adipogenesis disorders in SONFH-BMSCs.

Hsa-circ33287

Hsa-circ-33287 was the mostly increased circRNAs during osteogenesis of BMP2-induced maxillary sinus membrane stem cells (MSMSCs). Circ33287 promoted the osteogenic differentiation of MSMSCs by competitively binding miR-214-3p and thereby increased its target gene Runx3 expression. Runx3 could influence the expression of BMP9-induced osteogenic transcription factor and phosphorylation of smad1/5/8 [91]. Moreover, transplanting MSMSCs subcutaneously in mice exhibited that circRNA-33287 facilitated ectopic bone formation in vivo, while miR-214-3p suppressed that [40].

CircIGSF11

Zhang et al. discovered that circIGSF11(hsa-circRNA13685) could inhibit osteogenic differentiation of human BMSCs as a sponge of miR-199b-5p [38]. They carried out knockdown trials of circIGSF11 owing to its high abundance and overexpression of miR-199b-5p in view of its important role as enhancing osteogenic differentiation of BMSCs via modulating the GSK-3β signaling pathway [92]. Experiment results showed silence of circIGSF11 and overexpression of miR-199b-5p facilitated osteogenesis.

Others

There are several circRNAs involved in the differentiation of stem cells needing function validations and mechanism researches. CircBANP and circITCH were differentially expressed in the osteogenesis of PDLSCs. Bioinformatic analysis predicted circBANP and circITCH might bind to miRNA34a and miRNA146, respectively, and regulate osteogenesis through MAPK pathway [41]. Wang et al. researched stress-responsive circRNAs in PDLSCs and selected several representative circRNAs which might regulate miRNA-mediated osteogenesis of PDLSCs [29]. For example, circRNA5331 was detected to be in a high correlation with miR-204, which was elucidated to suppress the osteogenesis of mesenchymal progenitor cells by negatively regulating RUNX2 [93].

CircRNAs modulate proliferation and apoptosis in stem cells

Stem cells' ability of proliferation has close relationship with tissue regeneration [94]. So, it is important to understand the gene regulation in the proliferation and apoptosis of stem cells. We summarized circRNAs involved in proliferation and apoptosis of stem cells (Table 4). Firstly, we concluded circRNAs in myoblasts. CircZNF609 was characterized to modulate proliferation as knockdown of it in human myoblasts decreased proliferation markers like CDK1 and cyclin A2 [20]. Similar effects were observed in circZfp609

Table 4 CircRNAs modulating the proliferation and apoptosis of stem cells

Cell type	species	CircRNAs	Functions	Mechanisms	References
Myoblasts	Homo sapiens	CircZNF609	Promote proliferation	Unknown	[20]
	Mus musculus	CircZfp609	Promote proliferation	Unknown	[66]
	Gallus gallus	CircFGFR2	Promote proliferation	Sponge miR-133a-5p and miR-29b-1-5p	[68]
	Gallus gallus	CircSVIL	Promote proliferation	Unknown	[67]
	Bos taurus	CircFUT10	Inhibit proliferation and promote apoptosis	Sponge miR-133a	[70]
	Bos taurus	CircLMO7	Promote proliferation and inhibit apoptosis	Sponge miR-378a-3p	[71]
	Bos taurus	CircFGFR4	Promote apoptosis	Spong miR-107	[69]
BMSCs	Mus musculus	Mmu-circ-003795	Promote proliferation	Sponge mmu-miR-504-3p	[45]
	Mus musculus	Circ014511	Inhibit apoptosis	Sponge mmu-miR-29b-2-5p	[96]
PDLSCs	Homo sapiens	CDR1as	Promote proliferation	Sponge miR-7	[97]
HucMSCs	Homo sapiens	CDR1as	Promote proliferation and inhibit apoptosis	Unknown	[73]
HSCs	Mus musculus	Cia-cGAS	Inhibit proliferation	Sponge cGAS	[48]
MC3T3-E1 cells	Mus musculus	CircAFF4	Promote proliferation and inhibit apoptosis	Sponge miR-7223-5p	[98]

BMSCs bone marrow stem cell, *PDLSCs* periodontal ligament stem cells, *HucMSCs* mesenchymal stem cells derived from human umbilical cord, *HSCs* hematopoietic stem cells, *Cia-cGAS* circRNA antagonist for cGAS, *cGAS* cyclic GMP-AMP synthase

in mouse myoblasts [66]. CircFGFR2 and circSVIL were unlocked to promote the proliferation of chicken myoblasts [67, 68]. CircFGFR2 relieved the inhibition effects of miR-133a-5p and miR-29b-1-5p on proliferation as a miRNA decoy. However, the downstream reaction of these two miRNAs remained to be explored. Mechanisms of circSVIL on proliferation were unknown, but overexpression of it could result in more cells of S and G2/M phase and fewer of G0/G1, while knockdown of circSVIL exhibited inverse effects. CircFUT10 inhibited bovine myoblasts' proliferation and promoted apoptosis via binding to miR-133a and increasing SRF [70]. MiR-133 promoted myoblast proliferation by targeting SRF which is crucial for the growth of skeletal muscle [81, 95]. The authors speculated a regulation axis of circFUT10-miR-133a- SRF in muscle development. Like circFUT10, circFGFR4 accelerated bovine myoblasts apoptosis through sponging miR-107 and relieved its effects on Wnt3a [69]. CircLMO7 promoted the proliferation of bovine myoblasts and protected them from apoptosis through sponging miR-378a-3p.

Secondly, there are several circRNAs related to the proliferation and apoptosis of MSCs. CircRNA-014511 is an exonic circRNA located on chr4: 132656692-132673032 and was demonstrated to suppress apoptosis in mouse BMSCs receiving irradiation. A noteworthy downregulation of p53 and upregulation of anti-apoptosis factors Bcl-2 and Mcl-1 was observed and triggered by circ014511 through binding to mmu-miR-29b-2-5p [96]. MiR-29 family was believed to stimulate p53 expression and initiate the p53-mediated apoptosis in BMSCs [99]. In addition, p53 could suppress the transcription of Bcl-2 and induce G1 phase arrest in human non-small cell lung cancer cell lines cells after radiation [100]. Overexpressing circ014511 resulted in not G1 phase arrest but also G2 phase arrest in radiated cells. Circ014511 also changed the expression mode of other cell cycle-related proteins, like P21, GADD45A and Cyclin B1, and finally gave rise to radiation resistance in BMSCs [96]. Circ014511 held potential for becoming a novel target to protect and repair radiation damage in patients. More in vivo research should be carried out about this circRNA. Calcitonin gene-related peptide (CGRP) was demonstrated to enhance mouse BMSCs proliferation by upregulating mmu-circ-003795, which sponged mmu-miR-504-3p and released its target gene FOS like 2 AP-1 transcription factor subunit (FOLS2) [45]. FOLS2 and CGRP were both previously described to be associated with regulation of cell proliferation and differentiation [101, 102]. CDR1as was found to promote proliferation and inhibit apoptosis of HucMSCs with unknown mechanisms [73]. It also promoted the proliferation of PDLSCs under a lipopolysaccharide (LPS)-induced inflammatory condition via activating the ERK signal pathway as miR-7 sponge [97]. LPS contributed greatly to periodontitis [103]. The role of CDR1as in the proliferation of PDLSCs might provide a therapy clue in regenerating teeth and tissue damaged by periodontitis.

Finally, we picked up two circRNAs in MC3T3-E1 cells and HSCs. PIK3R1 activates downstream AKT by promoting the transformation of 4,5 phosphatidylinositol (4, 5)-bisphosphate (PIP2) to 3,4,5 phosphatidylinositol (3, 4,5)-trisphosphate (PIP3) [104]. Previous studies have shown that cell survival needs activation of the PI3K/AKT pathway [105, 106]. CircAFF4 could bind to miR-7223-5p to remove its inhibition of the downstream gene PIK3R. PIK3R1 could promote the proliferation of MC3T3-E1 cells and inhibit their apoptosis [98]. Mouse femoral fracture model confirmed that CircAFF4 promoted bone repair in vivo. This study provided a potential therapeutic target for the circRNAAFF4/ mir-7223-5p/PIK3R1 axis of action for fracture healing.

Long-term hematopoietic stem cells (LT-HSCs) were defined to possess the capacity of self-renewal and differentiation as an incessant supply of blood cells [107]. Cyclic GMP-AMP synthase (cGAS) was considered as a cytosolic DNA sensor and it could elicit production of cyclic GMP-AMP (cGAMP) upon binding DNA including self-originated DNA. CGAMP then activated the adaptor STING and catalyzed the synthesis of type I IFNs, driving HSCs into cycling and leading to HSC exhaustion [108]. CircRNA antagonist for cGAS (Cia-cGAS), originating from D430042O09Rik gene transcripts, was proved to bind nuclear cGAS and function as a cGAS sponge to prevent its combination with self-DNA with a stronger binding capacity. Cia-cGAS silenced original effects of cGAS and protected resting LT-HSCs from cGAS-mediated exhaustion [48]. Moreover, it was elucidated that the deficiency of the exonuclease TREX1 in human was linked to several autoimmune and inflammatory diseases [109]. Trex1-deficient mice caused raised expression of IFN-stimulated genes and cGAS deletion was recently reported to result in an elimination of pathological and molecular phenotypes in Trex1−/−mice [110]. This article also pointed out that overexpression of cia-cGAS in Trex1−/− bone marrow-derived macrophages could decrease IFN expression, implying cia-cGAS's suppression on the autoimmune signaling in Trex1-deficient cells. Consequently, cia-cGAS might be applied in therapy of hematopoietic malignancies or autoimmune diseases.

CircRNAs participate in the 'cross-talk' between stem cells and lymphocytes

Stem cells play a role in regenerative medicine in the form of being placed into a foreign tissue environment. So it is very important to study the interplay between stem cells and their microenvironment which maintains and regulates them [111].

Lgr5 $^{+}$ ISCs are a subset of ISCs expressing the G-protein coupled receptor Lgr5 as a specific marker and are detected to own the talent of long-term self-renewal and producing all epithelial cell types [112]. Innate lymphoid cells (ILCs) reside in the intestine niche and maintain local homeostasis through immune responses [113]. Published work showed that ILC2s (type 2 innate lymphoid cells) could secret IL-13 cytokine and IL-13 had many biological functions [114]. CircPan3 originated from the Pan3 gene transcript was unveiled to be abundant in both mouse and human Lgr5 $^{+}$ ISCs and regulate the stemness of ISCs [63]. CircPan3 bound to IL-13 receptor subunit (Il13rα1) mRNA in Lgr5P^{+} ISCs to facilitate its steadiness via competing with Ksrp, an RNA binding protein involved in mRNA decay [115]. Hence, circPan3 elevated expression of IL-13Rα1 on these cells. Subsequently, ILC2s secreted IL-13 to combine with IL-13Rα1 and activated STAT6 signaling, which further initiated the transcription factor FoxP1 and promoted the maintenance of ISCs.

MSCs suppressed the proliferation of T lymphocytes [116]. Psoriasis was an autoimmune skin disease [117]. Skin mesenchymal stem cells (sMSCs) in psoriatic lesions had weaker inhibition on T- cell proliferation [118]. Liu et al. analyzed RNA samples from normal skin and psoriasis lesions and then discovered that a circRNA located on gene chr2:206992521-206994966 was relevant to both psoriasis-related miRNAs and genes. Co-cultured experiments showed that T cells co-cultured with psoriatic sMSCs and chr2:206992521-206994966 knockdown sMSCs had alike proliferation activities which were more dynamic than those co-cultured with normal sMSCs, speculating that this circRNA participated in the pathogenesis of psoriasis through reducing sMSCs' ability to suppress T-cell proliferation. The pattern of cytokine secretion was also analyzed and it was found that knockdown sMSCs and psoriatic lesion-derived sMSCs had the similar mode: IL-11 secretion was elevated; IL-6 and hepatocyte growth factor were decreased in comparison with non-transfected normal SMSCs. Those are inflammation and immunomodulation-related cytokines, suggesting that this circRNA affected on cytokine secretion in sMSCs [55].

CircRNAs and cancer stem cells

Cancer stem cells are tumor cells exhibiting characteristics of stem cells such as self-renewal and differentiation capacities. These properties have been proposed to be responsible for the maintenance and the growth of tumors [119]. In 1994, Dick et al. isolated leukemia stem cells for the first time [120]. Following this landmark research, cancer stem cells were discovered in a variety of solid tumors [121–123]. Several researches gained insights into circRNAs regulating cancer stem cells.

CircZKSCAN1 was reported to suppress stemness of hepatocellular carcinoma cells (HCCs) through competitively binding to the RBP, fragile X mental retardation protein (FMRP). FMRP upregulated stemness in HCC cells by binding to cell cycle and apoptosis regulator 1 (CCAR1) mRNA and regulated its expression. CCAR1 was a co-activator of the Wnt/β-catenin signaling pathway [124] and was positively correlated with cell stemness in HCC through upregulating levels of active β-catenin. Absence of circZKSCAN1 was also proved to be related to worse prognosis, providing great clinical diagnostic and therapeutic potentials [125]. CircMALAT1 was highly expressed in HCCs from clinical hepatocellular carcinoma samples and was able to promote self-renewal of HCCs. CircMALAT1 performed this function not only by sponging miRNA but also by retarding mRNA translation like a brake, showing a dual-faceted pattern of circRNA-mediated post-transcriptional regulation of maintaining a specific cell state [126]. CircVRK1 was downregulated in breast cancer stem cells (BCSCs) compared to non-BSCSs and was able to inhibit the stemness of BCSCs. Bioinformatics analysis indicated that circVRK1 might regulate BCSCs through binding to miR-153, which needed more researches [127]. CircRNA hg19_circ_0005033 promoted proliferation, migration, invasion, and chemotherapy resistance of laryngeal cancer stem cells, proving clues for laryngeal squamous cell carcinoma therapy [128].

Conclusion and perspectives

In this review, we firstly discussed the general characteristics of circRNAs in the differentiation of stem cells and discovered that several circRNAs such as circFOXP1 could serve as stem cell biomarkers. Stemness and differentiation capacity are important characteristics of stem cells. We discussed two circRNAs which maintained stem cells pluripotency and participated in stem cells reprogramming: circFOXP1 and circBIRC6. Cell reprogramming is the ability to change a cell's fate to another one. Stem cell reprogramming can turn differentiated somatic cells into stem cells. Hence, circFOXP1 and CircBIRC6 might contribute to regenerative medicine via helping generate stem cells into clinical use. We then summarized key circRNAs involved in differentiation, proliferation and apoptosis of stem cells. CDR1as was proved to regulate adipogenesis, osteogenesis and myogenesis of multiple stem cells. It also intervened proliferation and apoptosis of stem cells. Therefore, CDR1as played a vital role in stem cells and might be a promising target of stem cell therapies. We also referred to two circRNAs involved in the 'cross-talk' between stem cells and

lymphocyte: circpan3 and circ2:206992521-206994966. Lymphokines are an important part of microenvironment and have been proved to regulate stemness of stem cells [129, 130]. Researches on the relationship between stem cells and immune cells deepened our understanding of stem cells self-renewal and autoimmune diseases.

CircRNAs have been shown to act as miRNA sponges, gene transcription regulators, protein translators, protein decoys or scaffolds and so on. Up to now, circRNAs' function as miRNA sponge has received the most attention\, we look forward to more regulation mechanisms of circRNAs in stem cells. Besides, the upstream mechanism of circRNAs remains largely unclear. Factors regulating circRNAs expression in stem cells leave too much to be desired. Furthermore, there are several circRNAs in the text with function prediction but short of deeper mechanism researches. For instance, CDR1as promoted proliferation and inhibited apoptosis of hucMSCs. However, how it worked still needed to be explored [73]. There is no standard nomenclature of circRNAs, resulting a chaotic naming phenomenon in this manuscript. A comprehensive database called circbank was presented recently, implementing an innovative naming system for human circRNAs according to their parental genes [131]. It will be better if all circRNAs be named according to one uniform standard.

The rapid development of gene researches has triggered urgent desire of RNA-based therapies such as RNA drugs, including short interfering RNAs and antisense oligonucleotides (oligos). The first antisense oligo approved by FDA in 1998 was Vitravene, which was intended for treatment of cytomegalovirus (CMV) retinitis patients. Since then, several oligos were approved including Macugen, Kynamro, Exondys 51, Defitelio, Spinraza [132]. 2018 had been extremely important for oligonucleotides with two FDA approvals. One was Patisiran, a double strand small interfering RNA (siRNA). Another was Inotersen, a single stranded 20-mer phosphorothioate antisense oligonucleotide. Both were prescribed for the cure of polyneuropathy hereditary transthyretin mediated amyloidosis in adults through suppression of mRNA and reduction of TTR protein [133]. In view of the abovementioned effects of circRNAs on stem cells, it is reasonable to expect the clinical use of circRNAs in stem cells associated therapies. Cell-specific circRNAs can be used as biomarkers to indicate the differentiation status of stem cells and distinguish them from differentiated cells. Tissue and disease-specific circRNAs can be explored for preclinical prediction of diseases or judging prognosis. Moreover, circRNAs may serve as therapeutic targets of diseases, or be used in tissue engineering together with stem cells or biomaterials in later clinical stages. For example, circNfix was demonstrated to weaken the cardiac regeneration regulated by super enhancer, providing a new therapeutic target of myocardial infarction [134]. In the future, researchers might explore the role of more circRNAs in the molecular regulatory network deeply, and apply more in vivo research to verify circRNAs' effects on stem cells, laying a foundation for transforming scientific research achievements into clinical application.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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