Review

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Circular RNAs and hereditary bone diseases

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Summary **Circular RNA (circRNA) is a non-linear form of RNA derived from exonic, intronic, and exon-intron gene regions. circRNAs are characterized by covalent closed loops, highly stable nuclease resistance, and specific expression in species and developmental stages. CircRNA molecules have been identified as playing roles in the regulation of cell transcription, transcriptional expression after translation, interactions with microRNAs, and protein coding. A high stability and tissue- and disease-specific expression allow circRNAs to serve as potential biomarkers both for diseases and prognosis. CircRNAs function in bone remodeling by directly participating in bone-related signaling pathways and by forming the circRNA-miRNA-mRNA axis. Studies have seldom reported on the low incidence of circRNAs in genetic bone disorders. The current study reviews the characteristics of circRNAs and recent research on their role in rare hereditary bone diseases.**

Keywords: Circular RNA, biogenesis, hereditary bone diseases, osteoblast, osteoclast

1. Introduction

Circular RNA (circRNA) is a non-linear form of RNA that was first discovered more than 40 years ago (*1*). As next-generation sequencing has appeared, tens of thousands of circRNAs have been identified (*2,3*). CircRNAs are predominately expressed in the cytoplasm and highly conserved among different species (*3*). Great numbers of the functions of circRNAs have been explored, including action as miRNA sponges, to regulate transcription, and protein and peptide coding (*4,5*). Many studies on circRNAs have involved cancer and other complex diseases, but rare hereditary bone diseases have seldom been reported.

Bone metabolism is related to both osteoblasts, which are responsible for bone formation, and osteoclasts, which are involved in bone resorption. An imbalance in bone homeostasis greatly affects bone health and induces related bone diseases. Hsa_circ_0019142 and hsa_circ_0005846 have been identified as regulators of osteoblast differentiation and are related to the Wnt signaling pathway. The spectrum of circRNA expression in different stages of osteoclast differentiation in mice has been reported, and this has provided fundamental data for study of the function of circRNAs in bone resorption. Further study of these rare genetic bone disorders would enhance understanding of their underlying mechanisms, potential molecular markers, and cures. Moreover, experience in dealing with these rare bone disorders could increase knowledge of more common bone diseases.

2. Circular RNA and its Features

2.1. *The Discovery of circRNA*

Noncoding RNA is a functional RNA molecule that is not translated into a protein. It is the main product of eukaryotic transcription, accounting for 95% of the total RNA of eukaryotic cells (*6*). Noncoding RNAs with regulatory roles are divided into two groups according to their chain length (*7,8*). Short chain non-coding RNAs are less than 200 nt in length and include

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small interfering RNAs, microRNAs (miRNAs), and Piwi-interacting RNAs, while long chain non-coding RNAs are longer than 200 nt and include circular RNAs (circRNAs).

CircRNAs were first discovered in RNA viruses during the 1970s (*2,3*). In the 1980s, they were identified in yeast mitochondria, hepatitis viruses, and humans (*9*). They are now known to be abundant in eukaryotes and protozoa (*10*).

The low copy number of circRNAs meant that they were first thought to be wrongly spliced mRNA, RNA processing byproducts, or viruses (*1*). However, subsequent studies found that endogenous circRNAs are stable, conserved non-random products produced by RNA splicing that play a role in controlling gene expression (*11*). As high-throughput technology has advanced and corresponding databases such as circBase, deepDase, and starBase have been created in the 21st century, the number of verified circRNAs has increased rapidly, with over 25,000 different types of circRNA being reported in human fibroblasts (*12*).

2.2. *Formation of circulation*

Different forms of circRNA have been identified: exon circRNAs, intron circRNAs, and exon–intron circRNAs (*13,14*). Most circRNAs consist of exons, some of which derive from encoded RNAs in 5' or 3' untranslated regions (UTRs), while others are from non-coded RNAs (*11,15*). There are two hypotheses for the formation of exon circRNAs. The first involves skipping of precursor RNA over a section of exons during transcription, followed by enzymatic shearing at both ends of this section, and the connection of the ends to form a lariat. The second hypothesis suggests that introns at both ends of the exon carry out base pairing during RNA transcription. The 3' end of the downstream exon connects to the 5’ end of the upstream exon to combine two introns, and then the cyclized exon is released as circRNA (*16*).

RNA polymerase cleaves the intron from pre-mRNA to form an annulus. The circRNA formed in this manner is known as circular intronic RNA (ciRNA) (*13*). ciRNAs mainly exist in the nucleus and participate in regulating the expression of their parent genes, instead of function as sponges. ciRNAs processing relies on a consensus motif containing a 7-bp 5' end with splice sites rich in guanine and uracil bases, a 7-nt GU-rich element near the 5′ splice site, and an cytosine-enriched area near the RNA shear branch sites of 11 bp in length (*14*).

Many circRNAs in the nucleus contain introns that have not been spliced. These are known as exon–intron circRNAs (EIciRNAs) and are found at many transcription sites. The removal of EIciRNAs reduces the expression of parental mRNA, indicating that they promote parental mRNA transcription (*13*).

2.3. *Characteristics of circRNAs*

The difference between circRNA and linear RNA is that the former is a closed annular structure without a 5' cap or a 3' poly A tail, and hence it is not readily degraded by exonuclease The inherent stability of this structure affords it an important role in internal homeostasis when faced with environmental challenges (*17,18*).

CircRNAs are found in eukaryotes (*11*), prokaryotic organisms (*10*), viruses (*19*), and Archaea (*20*). Most circRNAs exist in the cytoplasm of eukaryotic cells, although some are found in the nucleus (*1*). Their levels of expression are at least 10 times higher than those of their linear isomers (*12*), although expression varies among different animal tissues, with the highest being reported in the brain and blood (*13*). RNA samples from whole blood have been analyzed following the removal of ribosome RNA from total RNA, and more than 4,000 specific circRNA molecules have been identified using random primer inversion. These molecules were compared to the ENCODE database, and the expression of circRNAs in the blood was found to be higher than that in the liver and cerebellum (*16,21*).

In addition to their structural stability and widespread distribution, circRNAs are developmental-stage-specific. An analysis of human oocyte and preimplantation embryo transcription (*16*) indicated that most circRNAs are developmental-stage-specific (*22*) and that they are regulated dynamically. In the brain of Drosophila, some circRNAs increase with age (*23*). Nematodes contain thousands of circRNAs that differ in expression depending on the stage of growth or development.

CircRNAs are relatively conserved among species. For example, circRNAs in the human brain are similar to sequences in mice and Drosophila. Indeed, of the 1,903 circRNAs identified in mice, 81 are the same as sequences found in humans (*24*). One study found that 20.2% of pig circRNAs have direct human homologs, while 16.96% of pig circRNAs have direct mouse homologs (*25*). Another study found a direct homology between 29.4% of pig circRNAs in humans (*25*), while 1,510 circRNAs (25.45%) in mice and 5,189 circRNAs (87.44%) in humans were homologous to pig circRNAs. Sequential conservation analysis also indicated that circRNAs may have conserved functions in pigs, mice, and humans (*26*).

2.4. *Biological function of circRNAs*

CircRNAs contain miRNA binding sites, which make them competitive endogenous RNAs that can be used to isolate miRNA. For example, ciRS-7 with multiple tandem miRNA-7 binding sites can bind to miRS-7 *in vitro*. CircRNAs can also be used as endogenous "miRNA sponges" that inhibit normal miRNA function (*27*). miRNA sponges play a role in inhibiting miRNA and targeting gene binding. They can also be expressed

at different positions of the genome, so they can serve as an important component of the miRNA-mediated transcriptional regulatory network (*28*).

CircRNAs can be combined with proteins or used to influence RNA splicing, which indirectly affects protein function (*29*). For example, EIciRNAs combine with the U1 small nuclear ribonucleoprotein promote RNA polymerase II by interacting with its promoter to enhance gene transcription (*30*). The expression of mRNA encoded by the host gene was then reduced after removing EIciRNAs, suggesting that nuclear circRNAs have the potential to induce host genes to express themselves. However, not all EIciRNAs are located at transcription sites, so some may also modulate other parts of the genome. Notably, endogenous circRNAs are not associated with ribosome translation. Exogenous circRNAs are translated *in vitro* and *in vivo* through the internal ribosome entry site (IRES) or through the rolling-circle amplification mechanism (*31,32*), which amplifies short DNA or RNA into a longer strand.

CircRNAs play a similar role in association with mRNAs by combining with the translation initiation site or by destroying the integrity of mature linear RNA to prevent translation. For example, EIciRNAs interact with RNA polymerase and bind U1 snRNP to activate transcription of the parental gene, to inhibit RNA–protein interaction, and to regulate miRNA activity (*33*).

Recent studies have found that some circRNAs have a coding capability. For instance, Circ-ZNF609 encodes muscle differentiation-related proteins (*5*) generated from the second exon ring of its host gene with a 753-bp open reading frame. Its UTR elements rely on cis-control elements on the IRES sequence to initiate protein translation from the middle of circRNA (*32*), albeit at a lower rate than cap translation (*5,34,35*). CircRNA can also be used after N^6-methyladenosine modification in non cap-dependent translation (*36,37*). The N^6-methyladenosine zone identifies YTHDF3 proteins, binds to circRNA modified sites, and attracts eIF4G2 proteins and other translation initiation factors to drive circRNA translation (*38*). Some circRNAs also combine with ribosomes to form Rib–circRNA complexes that influence coding; their UTR regions have similar IRES translation-driven functions, but they have translation efficiency (*39*).

Intracellular circRNAs are secreted extracellularly. Their stability and prevalence in outer secretions and plasma (*40,41*) makes them suitable as potential disease markers. Compared to healthy individuals, patients with rectal cancer were found to lack 67 types of circRNAs and to possess 257 new forms. Moreover, the level of CircRNA-KLDHC10 expression in this cancer was significantly higher than that in normal serum (*42*), while the ratio of circRNA to linear RNA in MHCC Lm3-type hepatocellular carcinoma cells was six times higher than that in normal cells (*42*). Expression of hsa_circ_0000190 decreased significantly in the plasma and tissue samples of patients with gastric cancer (*43*), and hsa_circ_0000190 is a potential marker for gastric cancer because it is more sensitive and more specific than two traditional biomarkers, carcinoembryonic antigen (CEA) and CA19-9t. Together, these findings suggest that circRNAs could be used as reliable disease markers with which to diagnose certain cancers (*43*).

3. CircRNA and Hereditary Bone Disease

3.1. *CircRNA in osteoblasts and osteoclasts*

Osteoblasts are the main functional cells of bone formation and are responsible for the synthesis, secretion, and mineralization of bone matrix. During bone metabolism, osteoclasts bind to the target area and secrete proteases to dissolve bone minerals, digest bone matrix, and form bone resorption traps. Osteoblasts secrete bone matrix into the trap, and then perform mineralization to form new bone. Therefore, the balance between osteoclasts and osteogenesis is key to maintaining normal bone mass.

Osteoblast differentiation is regulated by a series of hormones, cytokines, and transcription factors (*44,45*). The transcription factor BMP2 belongs to the transforming growth factor beta superfamily and is one of the most important human cytokines. It induces heterotopic bone and cartilage formation and plays an important role in embryonic growth, cell growth and differentiation, bone development, and fracture repair. MC3T3-E1 cells treated with BMP2 had differential expression of 158 circRNAs, 74 of which were upregulated and 84 of which were downregulated in comparison to control cells. hsa_circ_0005846, hsa_circ_0019142, and hsa_circ_0010042 increased significantly following BMP2 treatment (*46*). hsa_circ_0005846 and hsa_circ_0019142 interact with 51 and 21 miRNAs, respectively, and both act as a sponge for miR-7067-5p. They are also involved in the FGF, EGF, PDGF, and Wnt signaling pathways, and they participate in cell growth and differentiation (*47*). BMP2 induces osteogenic differentiation *via* the hsa_circ_0019142/ hsa_circ_0005846 target miRNA–mRNA regulation network (*47*), in which the level of ALP, SP7, and RUNX2 mRNA expression increases significantly. Moreover, hsa_circ_0019142 interacts with miR-222-3p and miR-7067-5p (*48*), with the former functioning as an osteoclast inhibitor (*49*).

The expression of circRNAs is sequential in different stages of osteoclast development in mice. For example, of the 1797 circRNAs identified in mice, 147 were up-regulated in pre-osteoclasts, and 109 were down-regulated. In mature osteoclasts, 78 circRNAs were up-regulated, while 111 circRNAs and 94 miRNAs were up-regulated in activated osteoclasts (*50*). circRNA–miRNA synergistic regulation plays

an important role in osteoclast formation. miR-103 in the co-regulatory network was up-regulated by hsa_circ_0007873 and down-regulated by hsa_circ_0010763 and hsa_circ_0015622 (*51*). In addition, miR-335-5p directs the down-regulation of DKK1 (a Wnt inhibitor), it enhances Wnt signaling, and it promotes osteoblast formation and development (*52*), while miR-29a enhances osteoblast formation by regulating Wnt signaling through a positive feedback loop (*53*).

3.2. *CircRNA and osteoarthritis*

CircRNA is associated with a variety of diseases such as atherosclerosis and neurological disorders (*54,55*). However, its role in cartilage and bone and its effects on bone disease are rarely reported.

Osteoarthritis (OA) is a degenerative joint disease caused by cartilage degradation, bone thickening, and spur formation. A circRNA chip revealed differential expression of 71 circRNAs in patients with OA, including the up-regulation of 16 circRNAs such as hsa_circ_0100876 (circRNA-CER), hsa_circ_0101178, hsa_circ_01011914, and hsa_circ_0100086 while a further 55 were down-regulated. circRNA-CER can be up-regulated by cell interleukin-1 and tumor necrosis factor α, and it regulates the expression of MMP13 by endogenously competing with miR-136 to facilitate degradation of the chondrocyte extracellular matrix.

Wnt1 is the pathogenic gene for the autosomal-recessive form of osteogenesis imperfecta. A study that predicted circRNA interaction with miRNAs targeting Wnt1 found that hsa_circ_001042 interacted with miR-21, miR-148, and miR-152, and that it may functions in the MAPK signaling pathway. Has_circ00048 and 24 other circRNAs may serve as molecular sponges of miR-148 and miR-152 and may be involved in the focal adhesion pathway (*56*).

4. Conclusion

In conclusion, circRNAs are diverse, widely distributed molecules with stable structures and complex functions. Little is currently known about the association between circRNAs and hereditary bone disease, but our understanding of the role of miRNAs in hereditary bone disease has progressed considerably. For example, miR-222-3p and miR-7067-5p that are associated with osteoblasts are regulated by circRNA5846 and circRNA19142. Given the extensive interplay that exists between circRNAs and miRNAs, circRNAs are likely to control hereditary bone disease by interacting with miRNA or by their own ability to code protein. Therefore, new studies of circRNA will be crucial to the development of novel treatments. Future work should also examine the function of circRNAs in protein encoding and as miRNA sponges.

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