



Circular RNAs and Their Role in Pediatric Disease Pathogenesis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Circular RNA (circRNA) and long non-coding RNA (lncRNA) play a crucial role in gene regulation through microRNA (miRNA) pathways. Initially viewed as a molecular curiosity or a byproduct of RNA splicing processes, circRNAs were largely overlooked. Their biological relevance and diversity were only realised with the advent of high-throughput sequencing technologies in the 2010s. In this review manuscript, the role of circular RNA will be further evaluated in pediatric disease pathogenesis. Recent studies emphasise the importance of circRNA and lncRNA in competing endogenous RNA (ceRNA) networks in pediatric cancer. Circular RNA (circRNA) is a single-stranded RNA molecule that forms a closed loop structure, lacking 3' and 5' ends found in linear RNA. CircRNA has unique properties, including resistance to degradation and stability in cells. Some circRNAs are derived from protein-coding genes and have been shown to regulate gene expression. They have also been associated with diseases like cancer. In eukaryotes, genes are split by non-coding introns, and during RNA splicing, introns are removed, leaving only exons in the

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mature mRNA. Alternative splicing allows for different protein products from one RNA transcript. Exon scrambling, a non-canonical splicing event, can lead to different exon arrangements, impacting gene expression. Alu elements in flanking introns influence circRNA formation, and RNA editing can affect circRNA synthesis. CircRNAs can act as miRNA sponges, regulating gene expression. Genome-wide studies have identified circRNAs in various species, and their functions are still being explored. In recent years, circular RNAs (circRNAs) have emerged as key players in regulating cellular processes. Studies have identified specific circRNAs associated with NB progression. For instance, circAGO2 and circ-CUX1 have been linked to promoting growth and invasion of cancer cells by interacting with specific proteins. Moreover, Circ0093740 was identified as upregulated in WT samples, promoting proliferation and migration by sponging miR-136/145 and upregulating DNMT3A. Researchers found that SMN circ4-2b-3, detected in patient-derived serum exosomes, was associated with a strong response to Nusinersen in a subset of patients (Guerra et al. 2024). This suggests that SMN circ4-2b-3 could be a useful biomarker for predicting treatment response in type I SMA patients. Targeting circRNAs can be achieved using antisense oligonucleotides and silencing RNAs, with nanotechnology offering innovative delivery methods. CircRNAs are more stable than linear RNAs and have longer half-lives. They are predominantly found in the cytoplasm and may play roles in gene regulation and disease. Evolutionarily conserved circRNA mechanisms suggest their functional significance across species. CDR1as/CiRS-7 is an example of a circRNA that acts as a miRNA sponge, regulating gene expression. Wilms' tumour (WT) accounts for 6% of childhood tumours and 95% of pediatric kidney tumours. CircSLC7A6 was found to be upregulated in WT tumour samples, increasing cell apoptosis and repressing migration and invasion by targeting miR-107 and upregulating ABL2 expression. It was concluded that CircRNAs, stable and specific molecules involved in physiological processes and implicated in cancer, offer potential as clinical biomarkers and therapeutic targets in pediatric oncology.

Keywords: *Circular RNAs; non-coding RNA; pediatric disease; pathogenesis; Wilms Tumour; spinal muscle atrophy.*

1. INTRODUCTION

Circular RNA (circRNA) is a class of RNA molecules characterised by their circular structure. In contrast to linear forms of RNA, such as messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA), circRNAs form a closed, continuous loop. This structure gives them increased stability compared to linear RNA molecules. circRNAs were originally discovered in the 1970s, but it was not until the 2010s that their functions and significance in biological processes began to be fully recognised. Initially viewed as a molecular curiosity or a byproduct of RNA splicing processes, circRNAs were largely overlooked. Their biological relevance and diversity were only realised with the advent of high-throughput sequencing technologies in the 2010s. These technological advances allowed researchers to more closely examine the complexity of the transcriptome (the total set of RNA molecules in a cell) and demonstrate the presence and diversity of circRNAs in many organisms (Bessiere et al. 2025). circRNAs perform a variety of functions in the cell that are still the subject of intensive research. Many circRNAs can serve as molecular "sponges" for microRNAs

(miRNAs). By binding specific miRNAs, they can reduce the ability of these miRNAs to regulate their target mRNAs, leading to increased expression of the target genes (Nielsen et al., 2022). Some circRNAs can be transported to the cell nucleus, where they influence the transcription of certain genes, either by interacting with RNA polymerase II or other transcriptional regulators. circRNAs can also serve as binding partners for proteins, influencing their activity or localisation in the cell. Although it was long believed that circRNAs are non-coding, recent studies have shown that some circRNAs are capable of encoding proteins by utilising internal ribosome entry sites (IRES) (Miao et al., 2021). Again, Exosomal circRNAs offer several advantages, such as high stability, abundance, and long half-life. In addition to their aberrant expression in tumour tissues, exosomal circRNAs have been widely shown to be associated with the progression and clinical features of various cancers. They can serve as early diagnostic and prognostic markers for cancer (Zhang et al., 2023).

CircRNAs play a role in various physiological processes and are dysregulated in numerous diseases, including cancer, neurodegenerative

diseases, and cardiovascular diseases (Mo, 2023). Their stability and conserved expression in body fluids make them potential biomarkers for disease diagnosis and monitoring. CircRNAs are multifunctional molecules that have been shown to regulate gene expression transcriptionally and post-transcriptionally and exhibit distinct tissue- and development-specific expression patterns associated with a variety of normal and disease conditions, including cancer pathogenesis. Over the past years, due to their intrinsic stability and resistance to ribonucleases, particular attention has been drawn to their use as reliable diagnostic and prognostic biomarkers in cancer diagnosis, treatment, and prevention (Pisignano et al., 2023). Research on circRNAs is a rapidly growing field. Scientists are working to better understand the exact molecular mechanisms through which circRNAs exert their functions and further explore their potential use in biotechnology and medicine. Despite significant progress in recent years, much remains to be elucidated about the biological roles and the mechanisms of gene regulation by circRNAs. This review aims to evaluate the role of circular RNA in pediatric disease pathogenesis.

1.1 Circular RNA and Pediatric Cancer

With the advancements in high-throughput sequencing techniques, extensive studies are being conducted to understand the role of circRNAs in various diseases. Particularly, the relationship between circRNA and tumors cannot be ignored. Several studies have shown that circRNAs play a vital role in tumor occurrence, proliferation, metastasis, invasion, EMT, apoptosis, and cell cycle (Yu et al., 2021). CircRNAs play various roles in cellular functions, acting as miRNA and protein sponges, modulating transcription, and splicing (Galardi et al. 2022, Ahmadov et al. 2021, Latowska et al. 2020, Skrypek et al. 2020). Their aberrant expression in diseases suggests their potential as diagnostic and prognostic biomarkers due to their resistance to RNases. In cancer, circRNAs regulate tumour proliferation and invasion, making them promising therapeutic targets (De Tomi et al. 2024). Recent findings on circRNAs in pediatric solid cancers, including brain tumours, neuroblastomas, sarcomas, Wilms tumours, hepatoblastomas, retinoblastomas and gastric cancer were described (Wang et al. 2025, Lin et al. 2025, Li et al. 2025).

1.2 Circular RNA and Medulloblastoma

Medulloblastoma is a common malignant tumor in children affecting the central nervous system (Beylerli et al. 2025, Spinello et al. 2025, Nejadi Orang et al. 2024, Martinez de Estibariz et al. 2023, Liu et al. 2022, Rickert et al. 2021, Zhao et al. 2021). Despite advancements in traditional treatments like surgery, radiotherapy, and chemotherapy, some MB patients have a poor prognosis. Research is focusing on molecular targeted therapies to improve outcomes and reduce side effects. CircRNAs have emerged as potential targets in MB. Lv et al. identified circ-SKA3 and circ-DTL as differentially expressed circRNAs in MB compared to normal cerebellum tissues. Silencing these circRNAs suppressed cell proliferation, migration, and invasion in MB cell lines (Azatyan et al. 2022). Recent research found that circSKA3 promotes MB progression by sponging miR-383-5p, leading to FOXM1 regulation. Another study showed that circ-SKA3 decoys miR-326 to increase ID3 expression, promoting cell growth and invasion (Martinez de Estibariz et al., 2023). CircSKA3 was also linked to the miR-520 h/CDK6 axis in MB progression. These findings suggest circRNAs like circSKA3 play a role in tumour development and could be potential therapeutic targets.

1.3 Circular RNA and Neuroblastoma

Neuroblastoma (NB) is a common childhood cancer originating from primitive neuronal crest cells of the sympathetic nervous system, typically found in the adrenal medulla or paraspinal ganglia (Du et al. 2023, Fuchs et al. 2023, Karami Fath et al. 2022, Chen et al. 2023). It can either progress rapidly or resolve spontaneously, especially in infants. About 25% of cases present as a solitary mass treatable with surgery, while 60% have disseminated disease involving bone, bone marrow, lymph nodes, and liver. Patients with metastasis have poor survival rates. Despite advancements in understanding NB at a genetic and molecular level, the prognosis for metastatic disease remains grim. Research is ongoing to uncover mechanisms driving NB progression and identify new treatment targets (Zhang et al., 2025).

In recent years, circular RNAs (circRNAs) have emerged as key players in regulating cellular processes. Studies have identified specific circRNAs associated with NB progression. For instance, circAGO2 and circ-CUX1 have been linked to promoting the growth and invasion of

cancer cells by interacting with specific proteins. Other circRNAs like circDGKB and circCUX1 have been shown to influence glycolysis and aggressiveness in NB cells by modulating gene expression. Additionally, circRNAs targeting microRNAs, such as miR-16-5p and miR-388-3p, have been implicated in NB pathogenesis. Further research has revealed dysregulated circRNAs in NB cell lines, with some originating from amplified regions of the MYCN gene. These circRNAs are associated with key signalling pathways and processes like epithelial-to-mesenchymal transition. High-throughput sequencing studies have identified differentially expressed circRNAs in NB tumours, some of which target miR-21, a regulator of proliferation and apoptosis. Notably, circRNAs like circPDE5A and circ_0132817 have been found to modulate NB progression by regulating microRNAs and downstream targets like NOL4L. Recent studies have highlighted circRNAs like circ0125803 and circ_0135889 as potential regulators of NB progression through interactions with microRNAs and target genes. CircKIF2A has also been implicated in promoting NB cell aggressiveness by targeting PRPS1. These findings underscore the potential of circRNAs as biomarkers and therapeutic targets in NB, although further validation is needed. Ongoing research aims to elucidate the precise roles of circRNAs in NB pathogenesis and their therapeutic implications for individual patients.

1.4 Circular RNA and Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common soft tissue malignancy in children and adolescents, accounting for up to 3–4% of childhood cancer cases and approximately 50% of all sarcomas. Among the main RMS subtypes, embryonal (ERMS) and alveolar sarcomas (ARMS) account for 60% and 20% of all RMS cases, respectively. ARMS is associated with specific genetic alterations and generally has a worse prognosis due to its low response to treatment. In 2019, Rossi et al. found that circ-ZNF609 is upregulated in RMS cell lines, particularly in ARMS, and acts as a positive regulator of cell proliferation pathways. Knockdown of circ-ZNF609 induces a block of the G1–S transition, specifically in ERMS cells, with a decrease in p-AKT protein levels in both ERMS and ARMS cell types. Moreover, circ-ZNF609 is overexpressed in RMS primary tissues. In 2021, the same research group identified high expression of circVAMP3 in ARMS

cell lines and demonstrated its involvement in cell cycle progression through AKT-related pathways (Galardi et al., 2022). Downregulation of circVAMP3 leads to the upregulation of CDKN1A and WEE1, which regulate the CCNB1/CDK1 complex, controlling the G2/M checkpoint, and the downregulation of AKT and ERK1, resulting in cell accumulation in the G2 phase.

1.5 Circular RNA and Osteosarcoma

Osteosarcoma (OS) accounts for approximately 35% of primary malignant bone tumours, with its metastatic form having the lowest survival rate among all pediatric cancers (Liu et al. 2021, Zhang et al. 2023, Liu et al. 2024, Liu et al. 2023, Yang et al. 2023, Ren et al. 2019). MNAT1 protein is upregulated in OS tissues compared to normal bone tissue. Among the four miRNAs aberrantly expressed in OS and predicted to target MNAT1, miRNA-26a-5p shows a negative correlation with MNAT1 expression (Liu et al. 2024, Chen et al. 2022). The circRNA has_circ-0001146 promotes MNAT1 expression by sponging miR-26a-5p, leading to increased proliferation and invasion ability.

1.6 Circular RNA and Wilms Tumour

Wilms' tumour (WT) accounts for 6% of childhood tumours and 95% of pediatric kidney tumours (Shu et al. 2025, Tian et al. 2022). Circ0093740 was identified as upregulated in WT samples, promoting proliferation and migration by sponging miR-136/145 and upregulating DNMT3A. Conversely, has_circ_0008285 (circCDYL) was downregulated in WT tissues, suppressing proliferation, migration, and invasion by upregulating TPJ1 expression. CircSLC7A6 was found to be upregulated in WT tumour samples, increasing cell apoptosis and repressing migration and invasion by targeting miR-107 and upregulating ABL2 expression.

1.7 Circular RNA and Hepatoblastoma

Hepatoblastoma (HB) is a significant liver cancer in infants, representing about 1% of all pediatric cancers (Li et al. 2025). Current treatment methods for HB include surgical resection, adjuvant chemotherapy, and liver transplantation. However, a high percentage of patients face a risk of relapse or metastasis, with a mortality rate exceeding 35% in advanced cases. In the study of HB, researchers have identified several circRNAs with potential roles in the disease. For

example, circRNA has_circ_0015756 was found to be significantly upregulated in HB tissues and metastatic cell lines, and its silencing led to reduced cell viability, proliferation, and invasion. Predictive analyses suggested several miRNAs as potential targets of circ_0015756, with functional experiments confirming the regulation of circ_0015756 by miR-1250-3p (Wang et al., 2024). Other studies have highlighted the dysregulation of circRNAs in HB, such as has_circ_0000594 and circHMGCS1, which play roles in regulating tumour suppressor miRNAs and oncogenic pathways. Additionally, circ-STAT3 was identified as a promoter of HB tumour growth through its interaction with miR-29a/b/c-3p. Recent research has also explored the involvement of circRNAs in maintaining stemness in HB cells. CircRNA CDR1 and circSETD3 were found to influence stem cell populations and tumour progression in HB through interactions with miRNAs and downstream signalling pathways.

Overall, these studies shed light on the potential roles of circRNAs in HB pathogenesis and provide insights into novel therapeutic targets for this aggressive pediatric cancer (Li et al. 2022, Zhou et al. 2022).

1.8 Circular RNA and Retinoblastoma

Abnormal circRNA expression is closely linked to various ocular disorders, including retinoblastoma (RB), the most common eye cancer in children. Treatment approaches for RB have improved survival rates, but challenges remain in managing resistant disease. Understanding the molecular events in RB progression is crucial. Studies have shown that circRNAs like has_circ_0001649 play a role in RB development by regulating AKT/mTOR signalling. Other circRNAs, such as TET1-has_circ_0093996 and circTET1, impact RB progression by modulating gene expression and signalling pathways. Circ_0075804 and circ_ODC1 also influence RB cell proliferation through interactions with specific proteins and microRNAs. Additionally, circ_0000527, circ_0000034, circMKLN1, and circ-FAM158A have been implicated in promoting RB aggressiveness by regulating gene expression and cell growth (Asadi et al., 2022). Recent research has identified circ_0084811 as a potential regulator of RB cell proliferation and apoptosis by targeting E2F5 through miRNA sponging. Understanding the role of circRNAs in

RB pathogenesis could lead to novel therapeutic strategies for this cancer.

1.9 Circular RNA and Blood Cancer

This work is focused on the latest scientific evidence regarding circRNAs in solid pediatric tumours, but their role in blood cancers is also significant (Dashti et al. 2025, Filomena et al. 2024, Sun et al. 2024, Li et al. 2021, Tretti-Parenzan et al. 2024, Liu et al. 2023). CircRNAs can serve as clinical biomarkers for blood cancers due to their stability and abundance in bone marrow and body fluids (Poncelet et al. 2025, Wilson et al. 2024, Gutierrez-Camino et al. 2024, Liu et al. 2022, Babin et al. 2021, Liu et al. 2021). Several circRNAs have been identified as diagnostic and prognostic biomarkers in blood malignancies like multiple myeloma (MM), acute lymphocytic leukaemia (ALL), and juvenile myelomonocytic leukaemia (JMML) (Poncelet et al. 2025, Fu et al. 2023, Ye et al. 2023). For example, circRNAs involved in cell proliferation and tumor progression (e.g., circ-SMARCA5, hsa_circ_0007841) and chemoresistance (e.g., circRNA_101237) have been identified in MM. In ALL, circPVT1 was found to promote leukemogenesis, while circRNF220 was suggested as a prognostic biomarker in AML (Deng et al. 2023). CircMCTP, circLYN, and circAFF2 were upregulated in JMML, indicating their role in the disease. The search for circRNAs in blood cancers is still in its early stages but holds promise for identifying biomarkers.

1.10 Circular RNA and Spinal Muscle Atrophy (SMA)

Spinal muscular atrophy (SMA) is a neuromuscular disorder that affects α -motor neurons. Nusinersen, an antisense oligonucleotide, is used to treat SMA by correcting splicing defects in SMN2 (Wirth et al., 2021). Identifying biomarkers to predict treatment response in SMA patients is crucial. SMN circular RNAs (circRNAs) as potential biomarkers for SMA were found (Guerra M et al. 2024). In a recent study, conducted at Fondazione Policlinico A. Gemelli in collaboration with Catholic University of Sacred Heart, included 19 type I SMA patients treated with Nusinersen (Guerra et al. 2024). Researchers found that SMN circ4-2b-3, detected in patient-derived serum exosomes, was associated with a strong response to Nusinersen in a subset of patients (Guerra et al. 2024). This suggests that SMN

circ4-2b-3 could be a useful biomarker for predicting treatment response in type I SMA patients, although further research in larger cohorts is needed to confirm these findings (Guerra et al. 2024).

2. NANOPARTICLES AND CIRCULAR RNA DELIVERY

Anticancer therapy requires the development of new strategies, with circular RNAs (circRNAs) emerging as a promising molecular target (Raca et al. 2024). CircRNAs are stable single-stranded RNA molecules with joined 5' and 3' ends, playing a role in cancer progression (Wan et al., 2024). Targeting circRNAs can be achieved using antisense oligonucleotides and silencing RNAs, with nanotechnology offering innovative delivery methods. Research is focused on developing nanoparticles (NPs) with enhanced biocompatibility and targeting capabilities for circRNA therapy (25). These NPs have potential applications in imaging and gene therapy.

3. CONCLUSION

Recent advancements in high-throughput technologies like sequencing and omics have enabled the discovery of circRNAs, which are conserved endogenous RNAs with tissue-specific expression and diverse functions. Dysregulated circRNA expression has been observed in various cancers, indicating their potential as cancer biomarkers. While their exact roles in cancer development and progression are not fully understood, circRNAs show promise for clinical applications in cancer diagnosis, prognosis, and treatment. However, further research is needed to fully characterise circRNAs and their implications in cancer. It is unlikely that a single circRNA can serve as a universal cancer biomarker, so a panel of cancer-associated circRNAs may be more effective for predicting and monitoring cancer. This approach could be particularly valuable in pediatric cancer, where novel biomarkers are needed for accurate risk assessment. CircRNAs, stable and specific molecules involved in physiological processes and implicated in cancer, offer potential as clinical biomarkers and therapeutic targets in pediatric oncology. Moreover, they could play an important role in Hirschsprung disease, necrotising enterocolitis, asthma, bronchopulmonary dysplasia, ARDS and Kawasaki disease.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

As per international standards, parental written consent has been collected and preserved by the author.

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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