

Review Article

Novel Insights into the Role of circ-SHPRH in Human Malignant Disorders: Molecular Mechanisms and Clinical Relevance

Snur Rasool Abdullah ^{1,*} , Lina Abdelfattah Abdulrazak ² 

1 Department of Medical Laboratory Science, College of Health Sciences, Lebanese French University, Erbil, 44001, Iraq

2 Department of Biology, College of Education, Salahaddin University-Erbil, Erbil, 44001, Iraq

* Correspondence

snur.rasool@lfu.edu.krd

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Abstract

CircRNAs are a subclass of non-coding RNAs (ncRNAs) that participate in diverse biological processes, including protein interactions and the regulation of gene expression. The SHPRH gene, which encodes a protein crucial for DNA repair and the maintenance of genomic stability, also gives rise to a circular RNA known as circ-SHPRH. Evidence suggests that circ-SHPRH may interact with SHPRH mRNA and contribute to its stability, although the precise regulatory mechanisms remain under investigation. Recent studies suggest that circ-SHPRH may play an important role in the initiation and progression of cancer. Circ-SHPRH is reported to be downregulated in several cancer types, including gliomas, osteosarcomas, and lung cancer, and this reduced expression has been associated in some studies with poorer clinical outcomes and increased tumor aggressiveness. Studies in cell lines and animal models indicate that circ-SHPRH can function as a molecular sponge for specific microRNAs involved in tumor-related pathways, thereby influencing gene expression and cancer-related cellular phenotypes. These findings suggest that circ-SHPRH has potential value as a candidate biomarker for cancer diagnosis and prognosis; however, further clinical validation is required. Similarly, strategies aimed at modulating circ-SHPRH expression are being explored experimentally and may represent a potential therapeutic avenue in the future. In this review article, we summarize and critically discuss current evidence regarding circ-SHPRH and highlight its possible roles as a biomarker and regulatory molecule in cancer biology. Understanding the function of circ-SHPRH in different malignancies may improve insight into tumor-associated molecular mechanisms and could support the development of future diagnostic and therapeutic strategies.

Keywords: circ-SHPRH, Cancers, Biomarker, Therapeutic target.



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INTRODUCTION

Circular RNAs (circRNAs) are a group of ncRNAs that form covalently closed-loop structures, which distinguish them from the linear structure of most RNA molecules. They are created by back-splicing, which creates a circular molecule lacking a 5' cap and a 3' poly(A) tail by joining a downstream splice acceptor site to an upstream splice donor site¹.

CircRNAs are present in a wide variety of species and cell types and are now recognized

as a diverse subclass of ncRNA molecules with important biological roles². They are thought to be involved in the regulation of post-transcriptional genes, such as serving as miRNA sponges, controlling alternative splicing, and interacting with RNA-binding proteins (RBPs)³. It has also been demonstrated that some circRNAs are abundant and stable, which suggests that they may have potential applications as diagnostic and therapeutic biomarkers for several

diseases, although further validation is required. Meanwhile, it has been found that they are necessary for the control of gene expression as well as several biological processes⁴. One of the recently identified circRNAs is circ-SHPRH, which is derived from the SHPRH gene, a gene involved in DNA replication and repair⁵.

Circ-SHPRH (circ-2Traits ID: has-circ-001599, circ-Base ID: has-circ-0001649) is a circular RNA molecule that has recently attracted attention due to its potential involvement in several human malignancies, such as hepatocellular carcinoma⁶, liver cancer⁷, and cholangiocarcinoma⁸. It is generated through back-splicing of exons 26–

29 of the SHPRH gene (SNF2 histone linker PHD RING helicase), located at chromosomal region 6q24.3, producing a circular transcript of approximately 440 nt ^{9,10} (Figure 1). Evidence suggests that circ-SHPRH may regulate SHPRH gene expression, potentially forming a feedback regulatory loop during cancer development. The SHPRH gene encodes a DNA helicase and E3 ubiquitin ligase involved in maintaining genomic integrity and repairing DNA damage¹¹. Studies have demonstrated that reduced circ-SHPRH expression has been associated with genomic instability and cancer progression in several experimental models.

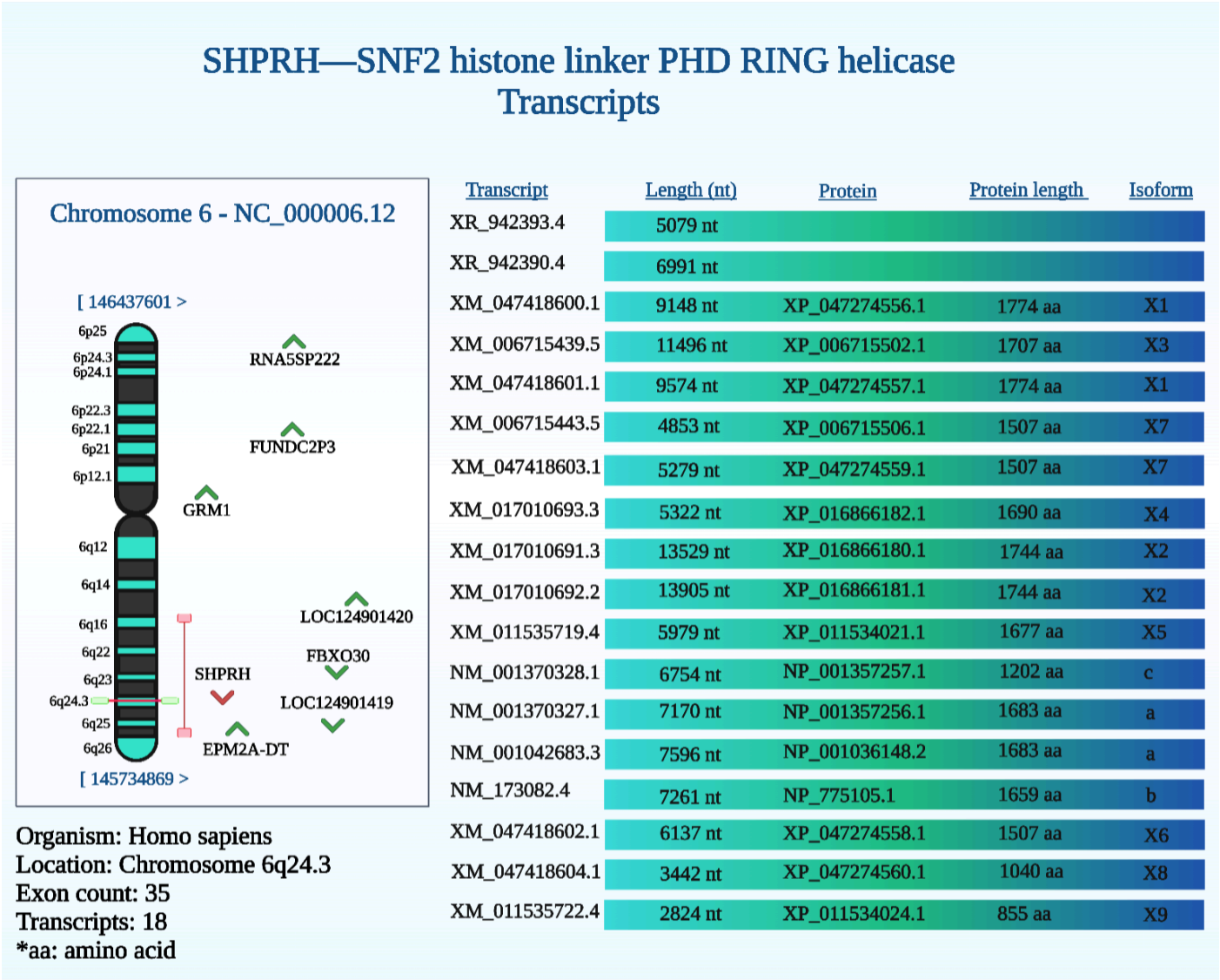


Figure 1. The schematic illustration represents the eighteen transcripts of the SHPRH gene and their corresponding protein isoforms and lengths.

Studies have shown that circSHPRH functions as a miRNA sponge, binding specific

microRNAs to regulate messenger RNA (mRNA) expression⁵. Circ-SHPRH can efficiently regulate the expression of several target genes, including those implicated in cancer development, by binding to miRNAs¹². Furthermore, current studies suggest that circ-SHPRH may participate in the regulation of DNA damage repair, an essential process for preserving genomic integrity and preventing tumor initiation¹¹. Many human diseases share the common feature of dysregulation of DNA damage repair, such as malignancy, ageing, and neurodegenerative illnesses¹³. Additionally, altered circ-SHPRH expression has been reported in several malignancies and may also be associated with drug resistance in certain experimental contexts¹⁴. It has been suggested that circ-SHPRH may influence drug resistance through modulation of apoptosis and DNA repair pathways, thereby promoting cancer cell survival.

Despite growing interest in circRNAs as regulatory molecules in cancer biology, the specific molecular roles and clinical relevance of circ-SHPRH across different tumor types remain incompletely characterized. Therefore, a comprehensive synthesis of current evidence is needed. Understanding the role of circ-SHPRH in human disorders and drug resistance may provide insight into its potential relevance for cancer diagnosis and management. In this review article, we summarize current findings on the cellular functions and molecular mechanisms of circ-SHPRH in different malignancies and discuss its possible value as a candidate biomarker and therapeutic target, while highlighting existing knowledge gaps and future research directions.

CIRC RNAS BIOGENESIS and FUNCTION

CircRNAs are a type of ncRNA molecule that creates a covalently closed and

continuous loop structure. They are produced by the back-splicing procedure from precursor mRNA (pre-mRNA)¹. During the process of back-splicing, a downstream 5' splice site (donor site) is covalently linked to an upstream 3' splice site (acceptor site) in the pre-mRNA molecule, resulting in circular RNA molecule formation¹⁵.

CircRNA biogenesis can occur through various mechanisms, including lariat-driven circularization, intron pairing-driven circularization, and RBP-mediated circularization¹⁶. Many factors control its synthesis, such as RBP, miRNAs, and secondary structures of RNA. These variables may have an impact on the pre-mRNA splicing pattern and circRNA synthesis. Circularization mediated by RBP is the first principle of circRNA biogenesis. Before this step, RNA polymerase II synthesizes the pre-mRNA from DNA¹⁷. Following that, the spliceosome splices the pre-mRNA, which is a complex of large ribonucleoproteins that removes introns and joins exons together to generate the mature mRNA. Then, circularization is mediated by RNA-binding proteins that recognize specific sequences and structures in the pre-mRNA¹⁸. RBPs bind to the flanking intronic regions of a pre-mRNA and promote circularization by bringing the splice sites nearby. As a result of this process, a circular RNA molecule is created without a 5' cap and a 3' poly(A) tail¹⁹ (Figure 2. a1). The second mechanism is intron pairing-driven circularization, in which circularization is driven through base pairing interactions between the complementary sequences within the flanking intronic regions of a pre-mRNA²⁰. This interaction brings the splice sites together and promotes circularization. Intron pairing-driven circularization can occur either in cis or trans²¹ (Figure 2. a2). Third, lariat-

driven circularization: in this mechanism, circularization occurs through the back-splicing of a lariat intermediate¹⁸. During the splicing process, the branchpoint adenosine of the intron creates a 2',5' phosphodiester bond with the 5' splice site, resulting in the formation of a lariat intermediate²². The 3' end of the intron then undergoes a second splicing

reaction, resulting in the secretion of the lariat intron and the production of a circRNA molecule²³ (Figure 2 b). Many biological processes have been revealed to be significantly influenced by circRNAs, such as gene regulation, RNA splicing, and protein translation²⁴, and their biogenesis is an active area of study in the field of molecular biology.

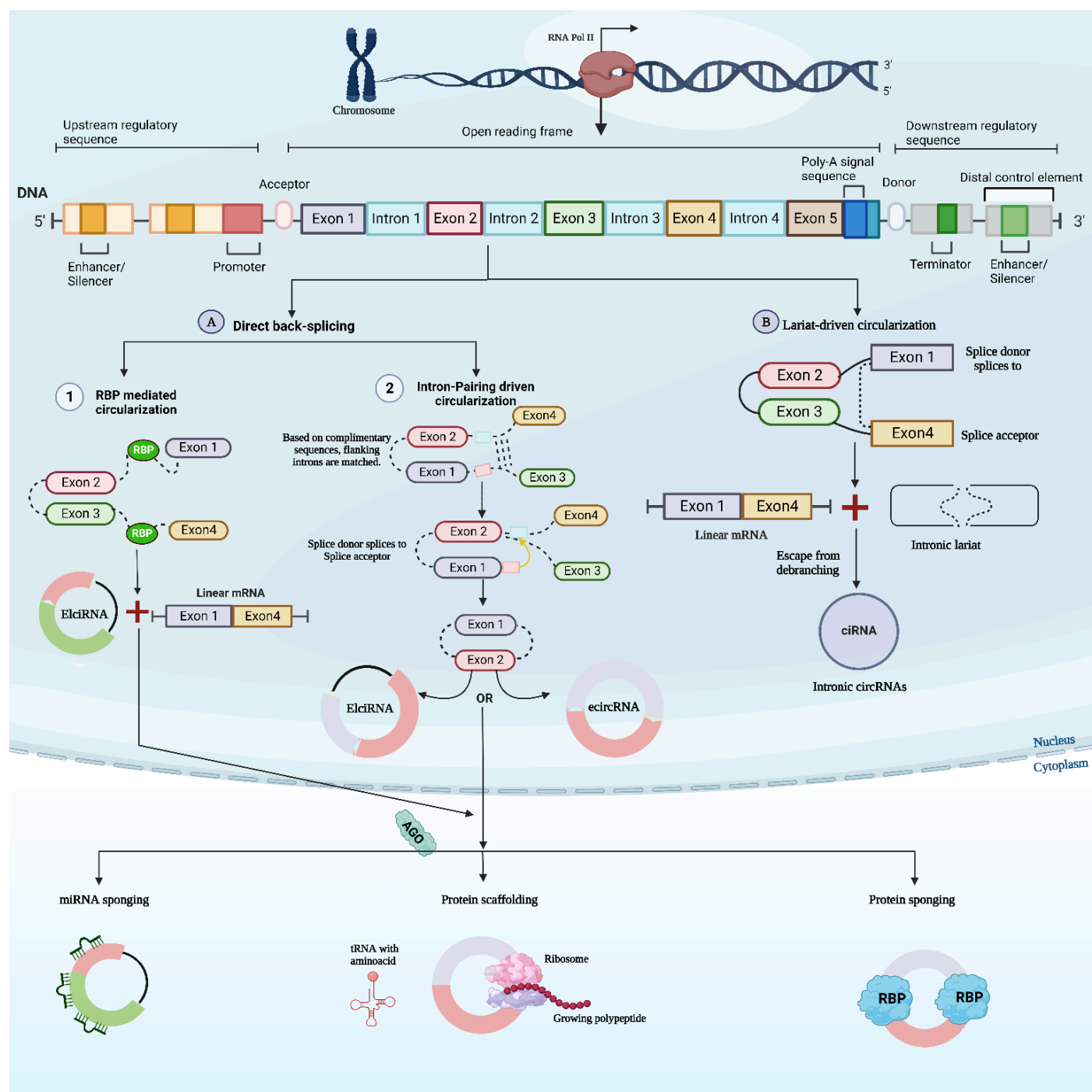


Figure 2. A schematic illustration described the mechanisms of circular RNA biogenesis and their essential function.

The circRNA's function is not yet fully understood, but studies have shown that they can control how genes are expressed by acting as regulators²⁵. For miRNAs and other

RBPs, circRNAs can serve as sponges, modulating their activity and downstream signaling pathways. Furthermore, circRNAs can regulate the splicing and transcription of

other genes by interacting with RBPs or serving as scaffolds for protein complexes²⁶. Briefly, research on the synthesis and function of circRNAs is currently ongoing. Additional studies are required to fully understand and pinpoint the range of roles that circRNAs play in gene regulation and cellular function.

CIRC-SHPRH'S STRUCTURE and FUNCTION

Circ-SHPRH is produced by the SHPRH gene on chromosome 6 in humans. It is created via back-splicing, which joins the 3' end of an upstream exon with the 5' end of a downstream exon²⁷. In contrast to RNAs' linear structure, which results in a covalently closed molecule with free ends, this circularization produces an RNA molecule that is more stable and resistant to exonucleases²⁸.

Circ-SHPRH has a dynamic, complicated structure that can take on several conformations based on the cellular environment and its binding partners¹¹. It has several RBP binding sites, including those for splicing factors and other regulatory proteins. According to certain research, circ-SHPRH can assemble RNA-protein complexes, which may play a major role in controlling the protein's biosynthesis, stability, and functionality. Although the exact role of circ-SHPRH is still unknown, recent studies have demonstrated its criticality for regulating the cell cycle and averting genomic instability²⁹. It has been demonstrated that circ-SHPRH specifically interacts with SHPRH and inhibits the E3 ubiquitin ligase activity, which is necessary for DNA replication and repair¹¹. Circ-SHPRH may assist in preventing DNA replication mistakes and protecting the genome from destruction by suppressing SHPRH gene activity³⁰. Additionally, circ-SHPRH has been shown to interact not just with SHPRH but also with

RBPs and splicing factors, among other proteins¹¹. These interactions might play a major role in regulating the biogenesis of circ-SHPRH or in affecting the way other genes and pathways function within the cell. Moreover, it has been demonstrated that circ-SHPRH functions as a miRNA sponge to control the expression of other genes³¹. MiRNAs specifically bind to circ-SHPRH and are then unable to bind to their intended mRNA targets, which results in the modulation of downstream gene expression and pathways³¹. This function implies that circ-SHPRH may have a variety of roles in maintaining cellular homeostasis and post-transcriptional gene regulation.

In brief, circ-SHPRH appears to be a complex and multifunctional molecule that may be involved in the regulation of post-transcriptional gene regulation, cell cycle progression, and genomic stability. However, further research is necessary to fully understand the mechanisms of action of circ-SHPRH as well as any possible therapeutic and diagnostic implications.

MALIGNANT DISORDERS

Circ-SHPRH has been extensively studied in malignant disorders, particularly in various types of cancer. Many types of cancer have been shown to have dysregulated circ-SHPRH, such as LC, HCC, CRC, and glioma, among others.

Dysregulation of Circ-shprh in Vitro, in Vivo, and Clinical Samples

Circ-SHPRH has been extensively studied in cell lines, animal models, and clinical samples to investigate its role in various diseases, particularly cancer (Table 1). In cell line studies, circ-SHPRH is downregulated in cancer cells compared with normal cells and acts as a tumor suppressor. According to Zhang et al., glioblastoma cells express circ-SHPRH at a lower level compared to

adjacent normal brain tissues and have a 440 nt. They used deep RNA-seq with rRNA suppression to find protein-coding circRNAs. By using targeted mass spectrometry and LC-MS, the authors further confirmed that circ-SHPRH was translated into a functional SHPRH protein of 144 amino acids⁵. Since full-length SHPRH protein expression increased after circ-SHPRH overexpression, it appears that circ-SHPRH protects or stabilizes full-length SHPRH. Similarly, Li et al. discovered that circ-SHPRH expression was markedly diminished in GC tissue relative to their corresponding para-cancerous histologically normal tissues. The expression level of circ-SHPRH exhibited a substantial correlation with pathological differentiation, suggesting its potential as a new biomarker for the diagnosis of GC³². Likewise, Zhang et al. demonstrate that circ-SHPRH expression is repressed in glioblastoma, the SHPRH-146aa overexpression in U373 and U251 glioblastoma cells reduces their tumorigenicity and malignant behavior *in vivo* and *in vitro*⁵.

Furthermore, studies have shown that overexpression of circ-SHPRH can inhibit the growth and proliferation of cancer cells, suggesting that it acts as a tumor suppressor. For example, Zhou et al. showed that miR-224-5p was sponged by overexpression of circ-SHPRH to control QKI expression in BEAS-2B cells during cadmium treatment, preventing the transformation caused by cadmium⁹ (Figure 3a). Similarly, Su et al. revealed that circ-0001649 acts as a ceRNA to sponge miR-612, miR-4688, and miR-127-5p, thus activating SHPRH to suppress hepatocellular carcinoma progression³¹ (Figure 3b). Likewise, circ-SHPRH overexpression acts as a sponge for miR-942 and increases the production of BARX2, which blocks the Wnt/ β -catenin

signaling pathway to slow bladder cancer (BCa) development³³ (Figure 3c). In addition, in osteosarcoma, Sun et al. revealed that circ-0001649 could suppress survival and viability, as well as induce apoptosis by activation of the STAT signal pathway in HOS and U2OS cells through sponging of miR-942, miR-338-5p, and miR-647³⁴ (Figure 3d).

In animal models, circ-SHPRH is dysregulated in various types of cancer. Studies have shown that circ-SHPRH can act as a sponge for miRNAs, which are small RNA molecules that play important roles in post-transcriptional gene regulation. For instance, circ-SHPRH acts as a ceRNA to sponge miRNA-127-5p, miRNA-612, and miRNA-4688; this inhibits the progression of HCC by activating SHPRH³¹. Similarly, according to a study using BALB/c nude mice, circ-SHPRH works as a sponge for miRNA-942 to stop the progression of BCa by upregulating BARX2 expression and suppressing the Wnt/ β -catenin signaling pathway³³.

In clinical samples, there have been some studies investigating the expression of circ-SHPRH in clinical samples of several types of cancer. For instance, in NSCLC, circ-SHPRH expression was found to be significantly decreased in tumor tissues compared to adjacent normal tissues. Low circ-SHPRH expression was also associated with advanced positive lymph node metastasis, TNM stage, and unfavorable prognosis⁷. Similarly, in CRC, circ-SHPRH expression was significantly decreased in tumor tissues compared to normal tissues, and low circ-SHPRH expression was correlated with pathological differentiation³⁵. Moreover, Hung et al.'s findings suggest that in OSCC patients, low plasma has-circ-0001649 was associated with patient recurrence and a poor prognosis³⁶. Thus, has-circ-0001649 can

be identified as the potential biomarker in plasma to provide information about the entire oral cavity in addition to the tumor, thereby providing a prediction for early recurrence and the second main OSCC³⁶. Overall, the predictive biomarker has-circ-0001649 may be a useful treatment target for RB. Overall,

dysregulation of circ-SHPRH in cell lines, animal models, and clinical samples suggests that circ-SHPRH may play a critical role in the development and progression of various diseases, particularly cancer and drug resistance, and may serve as a potential diagnostic and therapeutic target.

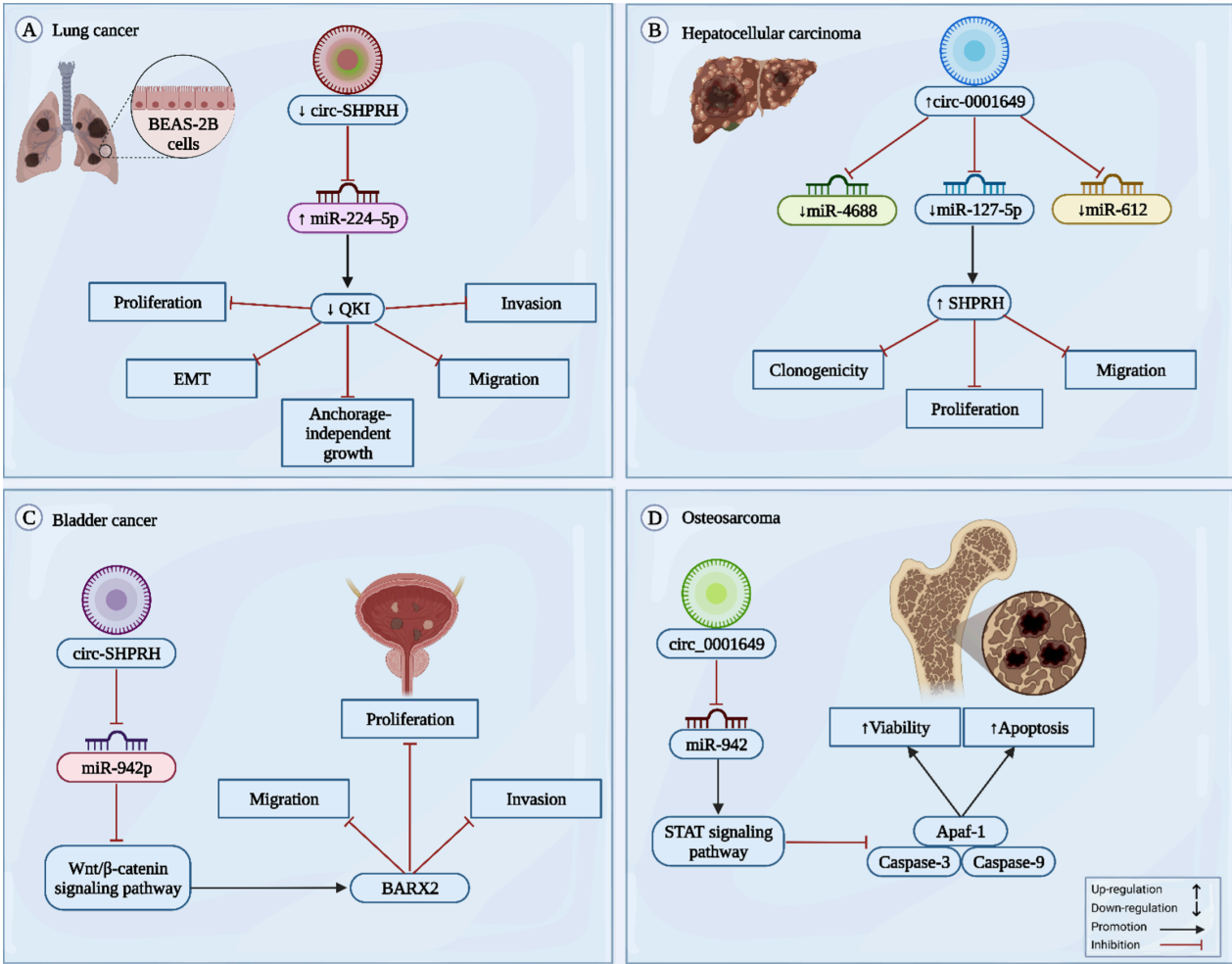


Figure 3. The schematic diagram represents the circ-SHPRH axis in different cancers. (A) In LC, circ-SHPRH sponges miRNA-224-5p to regulate the expression of the QKI gene, further preventing cell proliferation, anchorage-independent growth, migration, invasion, and EMT. (B) In HCC, competitively bound circ-0001649 binds to miRNA-612, miRNA-4688, and miRNA-127-5p, resulting in SHPRH upregulation. Furthermore, circ-SHPRH upregulation prevents the proliferation, migration, and clonogenicity of HCC cell lines. (C) In BCa, circ-SHPRH reduced the proliferation, migration, and invasion of tumor cells through miRNA-942P sponging, resulting in the inhibition of the Wnt/β-catenin axis and the upregulation of BARX2 expression. (D) Circ-0001649, through sponging miRNA-942, miRNA-647, and miRNA-338-5p, prevents cell proliferation of OS and the STAT pathway and induces apoptosis.

Table 1. Circ-SHPRH in the cell line, animal, and clinical studies, with their expression, which has clinical significance and may be used as a biomarker in different types of cancer.

Types of cancer	Roles/ Expression	Functional activities	Target miRNA/ related genes and signaling pathway	Cell line (in vitro) study	Animal (in vivo) study	Clinical study	Associated phenotype with dysregulated Circ-SHPRH	Clinical Importance	Ref.
Lung cancer	Tumor-suppressing/ downregulated	Proliferation, viability migration and invasion	miRNA-338-5p, miR-331-3p	H1581, A549, H1299, H358, 16HBE	BALB/c nude mice	53 paired sample	Lymph node metastasis, TNM stage	Prognostic , biomarker	7
	Tumor-suppressing/	Proliferation, migration and	miRNA-224-5p/ QKI	BEAS-2B	-	-	-	-	9

Types of cancer	Roles/ Expression	Functional activities	Target miRNA/ related genes and signaling pathway	Cell line (in vitro) study	Animal (in vivo) study	Clinical study	Associated phenotype with dysregulated Circ-SHPRH	Clinical Importance	Ref.
	downregulated	invasion, EMT							
Hepatocellular carcinoma	Tumor-suppressing/ downregulated	Tumorigenesis, metastasis	-	HCC-LM3, MHCC-97L	-	89 paired samples	Pathological differentiation	Diagnosis, Biomarker	⁶
	Tumor-suppressing/ downregulated	Proliferation, apoptosis, migration and invasion	-	MHCC97L, HepG2, HCCLM, HCCLM9	-	77 paired samples	Lymph node metastasis, TNM stage	Diagnosis, Biomarker	³⁷
	Tumor-suppressing/ downregulated	Proliferation, cell viability, migration	miR-4688, miR-127-5p, miR-612	SMMC-7721, H-97, HHCC, HepG2, HL-7702, HuH-7, Li-7, HepG2.2.15	Nude mice	84 paired sample	Tumor satellite, grade of differentiation	-	³¹
Gastric cancer	Tumor-suppressing/ downregulated	-	-	SGC-7901	-	76 paired sample	Pathological differentiation	Diagnosis, Biomarker	³²
	Tumor-suppressing/ downregulated	Proliferation, migration, and invasion, Viability	miRNA-20a	GES-1, SGC-7901, MKN28, AGS, MKN28, MKN45	-	25 sample	-	Diagnosis, Biomarker	³⁸
Cholangio carcinoma cells	Tumor-suppressing/ downregulated	Proliferation, Migration, invasion	-	RBE, HCCC-9810, HuCCT1, CCLP1, Huh-28, QBC939, KMBC, HIBEC	BALB/c nude mice	532 sample	Tumor size, Lymph node invasion, TNM stage, differentiation grade	-	⁸
Pancreatic ductal adenocarcinoma	Tumor-suppressing/ downregulated	Proliferation, colony-formation, apoptosis	-	PANC1, SW1990, BxPC3, Capan-2, HPDE	-	58 paired sample	Grade of differentiation, tumor stage	Prognostic Biomarker	³⁹
Retinoblastoma	Tumor-suppressing/ downregulated	Proliferation, apoptosis	AKT/ mTOR signaling	HXO-RB44, ARPE-19, SO-Rb50	Nude mice	60 RB tissues + 6 control	IIRC stage, tumor size	Prognostic Biomarker	⁴⁰
Glioma	Tumor-suppressing/ downregulated	Cell proliferation, cell apoptosis	Caspase-9, Caspase-3, Bax, Bcl-2	U118, U87 MG, LN229, U251, NHA	BALB/c nude mice	64 paired sample	WHO grade, Tumor size	Prognostic Biomarker	⁴¹
	Tumor-suppressing/ downregulated	Proliferation, tumorigenicity	-	-	nude mice	60 sample	-	Prognostic Biomarker	⁵
Osteosarcoma	Tumor-suppressing/ downregulated	Cell apoptosis, cell viability	miRNA-942, miRNA-647, miRNA-338-5p / CDK6, Apaf-1, CDK4, STAT3, Caspase-9, STAT5, Caspase-3, STAT signaling pathway	MG63, U2OS, HOS, Saos-2	-	26 paired sample	-	Prognostic Biomarker	³⁴
Bladder cancer	Tumor-suppressing/ downregulated	Cell proliferation, invasion, migration	miRNA-942/ BARX2, Wnt/ β -catenin pathway	EJ, T24, SV-HUC-1,5637, J82, UM-UC-3	BALB/c nude mice	-	T-stage, lymph node metastasis	-	³³
Oral squamous cell carcinoma	Tumor-suppressing/ downregulated	Tumor growth	-	OECM1	-	66 OSCC sample + 30 control	lymph node metastasis	Prognostic biomarker	³⁶
Colorectal cancer	Tumor-suppressing/ downregulated	Tumorigenesis	-	H116	-	64 paired sample	Pathological differentiation	Biomarker	³⁵

CIRC-SHPRH-RELATED SIGNALING PATHWAY in HUMAN CANCER

Numerous signaling pathways associated with the onset and advancement of cancer have been connected to circ-SHPRH. One such pathway is the Wnt signaling pathway. Wnt signaling is frequently dysregulated in cancer and is involved in a variety of biological processes, such as cell division, migration, and proliferation³⁷. Studies have shown that knockdown of circ-SHPRH activates the Wnt/ β -catenin pathway by regulating *BARX2* expression. Taken together, Zuo et al.'s findings revealed that circ-SHPRH serves as a miRNA-942 sponge to prevent BCa progression via *BARX2* upregulation, thereby suppressing the Wnt/ β -catenin signaling pathway³³. One more pathway is the STAT signaling pathway in osteosarcoma. Sun et al. found that circ-SHPRH promoted cell death through sponging of miRNA-338-5p, miRNA-647, and miRNA-942, as well as suppressed the STAT pathway and osteosarcoma cell proliferation³⁴. Further, circ-0001649, which controls cell growth and death through the AKT/mTOR pathway, is downregulated, which implies a poor prognosis for retinoblastoma⁴².

Overall, these findings suggest that circ-SHPRH may be extremely important in the initiation and development of human cancer by regulating several key signaling pathways that participate in cell differentiation, proliferation, and survival. To fully comprehend the processes of action and possible clinical applications of circ-SHPRH in cancer therapy, further research is required.

DIAGNOSTIC and THERAPEUTIC POTENTIAL of CIRC-SHPRH

Circ-SHPRH, as a non-coding RNA, can be a cancer therapeutic and diagnostic target. Numerous studies on different cancer types have found dysregulated expression of circ-SHPRH, which suggests that circ-SHPRH

could be a useful biomarker for cancer diagnosis. For example, the expression level of circ-SHPRH, which is diminished in HCC, has been shown to correlate with lymph node metastases, TNM stage, and patient prognosis⁴³. Additionally, GC shows higher circ-SHPRH expression, which has been linked to pathological differentiation³². According to these findings, circ-SHPRH may be used as a diagnostic marker in different kinds of cancer. Circ-SHPRH is a promising therapeutic target due to its role in regulating numerous signaling pathways linked to cancer development and progression. Numerous studies have shown that changes in the expression levels of circ-SHPRH can impact the migration, invasion, and proliferation of tumor cells. For instance, it has been demonstrated that overexpression of circ-SHPRH inhibits the spread and invasion of bladder cancer cells in both in vivo and in vitro³³ models. Furthermore, it was found that glioma cell migration and proliferation were increased by circ-SHPRH knockdown⁴⁰. These results suggest that circ-SHPRH could be a promising target for cancer therapy. However, further investigation is needed to understand fully the mechanisms of circ-SHPRH in cancer and to develop safe and effective therapeutic strategies.

THERAPEUTIC TARGETS

Research has shown the tumor-suppressive characteristics of circ-SHPRH, and enhancing their expression may provide an innovative therapeutic approach for cancer treatment. CircRNA expression can be increased by a variety of therapeutic strategies, such as CRISPR/Cas9 genome editing⁴¹, small molecule drugs⁴⁴, antisense oligonucleotides (ASOs)⁴⁵, and gene therapy⁴⁶. Exosomes and nanoparticles have been widely employed as delivery vehicles because

of their capacity to increase cellular absorption and prevent the therapeutic cargo from degrading to transport these molecules to the target site. Numerous investigations have confirmed the effectiveness of ASO delivery using nanoparticles⁴⁷ to boost the expression of circ-SHPRH in the tumor mass.

For example, artificially synthesized compounds known as ASOs can attach to particular sequences of RNA and cause splicing modification or RNA destruction. ASOs can be made to specifically target the circ-SHPRH intronic or exonic regions to encourage splicing and circularization, which will boost circ-SHPRH expression¹⁷. Additionally, ASOs can be engineered to attach to the RNA-binding proteins that control and stabilize the expression of circ-SHPRH⁴⁸. Likewise, splicing and circularization of circ-SHPRH can be induced by CRISPR-Cas9, leading to elevated expression⁴⁹. Alternatively, it can be applied to boost the expression of circ-SHPRH by deleting or altering the regulatory sequences that regulate its expression.

Furthermore, using synthetic circRNAs is another method of producing more circ-SHPRH. One strategy for creating a synthetic circRNA to boost circSHPRH expression would be to first determine the circSHPRH sequence and then make changes to improve its expression, stability, and functionality. To enhance stability and expression, the synthetic circRNA can be engineered to match the endogenous circSHPRH⁵⁰ sequence. Another strategy is to create a synthetic circRNA that targets and sequesters miRNAs that control the production of circ-SHPRH. The synthetic circRNA can indirectly upregulate circ-SHPRH expression by sequestering these miRNAs⁵¹. Moreover, gene therapy involves delivering beneficial genes to tissues or cells to treat or

prevent disease. The expression of the circ-SHPRH gene may be enhanced by introducing it into cancer cells, which may decrease tumor growth⁵². It should be noted that while these approaches hold promise for increasing circ-SHPRH expression, more research is needed to validate their effectiveness and safety in the context of cancer therapy.

CONCLUSION and FUTURE PERSPECTIVES

Circ-SHPRH is an emerging biomolecule that has been demonstrated to be involved in cancer progression, and current evidence from several studies suggests that it predominantly functions as a tumor suppressor in multiple malignancies. Studies have demonstrated that circ-SHPRH may inhibit tumor growth by regulating gene expression associated with tumor cell proliferation, DNA damage repair, and apoptosis-related pathways. Therefore, modulation of circ-SHPRH expression represents a potential therapeutic strategy; however, most supporting evidence is currently derived from experimental studies and requires further clinical validation. Several strategies, such as ASOs, miRNA-based approaches, and circRNA sponges, are being explored.

Despite the advancements achieved in our comprehension of the function of circ-SHPRH in cancer, several unanswered concerns and challenges remain. Further research is needed to identify additional circ-SHPRH targets and elucidate their roles in cancer development. Importantly, larger clinical cohort studies and additional mechanistic investigations are required to confirm its biological and clinical relevance across different tumor types. Also, the clinical success of circ-SHPRH-targeting strategies will depend on improvements in delivery efficiency and specificity. There is still more research required to completely understand

the mechanisms underlying the regulation of circ-SHPRH expression. Moreover, the creation of diagnostic tools to identify patients who might benefit from circ-SHPRH-targeted therapy, as well as the planning of clinical trials to assess the treatment's safety and efficacy, will be necessary before circ-SHPRH can be considered for routine clinical application.

However, future discoveries about circ-SHPRH may have important implications for cancer treatment strategies. The effectiveness of current cancer medicines may potentially be improved by the development of safe and efficient circ-SHPRH-targeting techniques, and the introduction of circ-SHPRH-targeted therapy into clinical practice will depend on further preclinical and clinical validation. Thus, more well-designed experimental and clinical research on circ-SHPRH is necessary to completely comprehend its function in cancer and support the development of evidence-

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Conflict of Interest

The authors declare no conflict of interest.

Use of Generative AI

Generative AI tools were used only for language improvement and proofreading. The authors reviewed and approved the final content and take full responsibility for the manuscript.

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