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REVIEW REPORT

A gene modifier, circSMARCA5, acts on breast and lung cancer stem cell dynamics and therapeutic targeting

Awjad Almotari[1,2], Bahauddeen M. Alrfaei[2,3*], Amani A. Alghamedi[1], Abir A. Alamro[1]

ABSTRACT

The SWItch/Sucrose Non-Fermentable chromatin remodeling complex, particularly the SMARCA5 gene and its product circSMARCA5, holds significant implications for understanding nucleosomal transformations, gene regulation, and cancer development. Additionally, the concept of cancer stem cells (CSCs) and their role in malignancies sheds light on the complex nature of cancer progression and the potential for targeted therapeutic interventions. The circSMARCA5 expression showed a significant and opposite association with its parent gene in breast cancer, indicating its potential as a therapeutic target for breast cancer treatment. CSCs in breast cancer share similarities with normal stem cells and exhibit disrupted signaling pathways, emphasizing the importance of identifying CSCs for understanding disease biology and developing targeted therapies. Additionally, research revealed circSMARCA5 expression is reduced in nonsmall cell lung cancer (NSCLC), and its overexpression impedes the proliferation, migration, and invasion of NSCLC, indicating its potential as a prognostic indicator for lung cancer patients. The CSCs have been identified in small cell lung cancer, contributing to tumor development, treatment resistance, and potential metastasis through the process of epithelial-mesenchymal transition, and are characterized by the overexpression of specific signaling pathways and cell surface markers. The current understanding of circSMARCA5's role in breast and lung malignancy highlights its significant contribution to tumor development and potential clinical applications, paving the way for promising therapeutic interventions in cancer treatment. This opens new avenues for personalized medicine and novel strategies for cancer management in the future.

Keywords: circSMARCA5, mircoRNAs, cancer stem cell, epigenetic.

Introduction

Cancer remains a formidable global health challenge, accounting for significant morbidity and mortality worldwide. In 2020 alone, cancer was responsible for an estimated 19.3 million new cases and nearly 10 million deaths, making it the second leading cause of death globally (1). Breast and lung cancers are among the most prevalent malignancies, with breast cancer surpassing lung cancer as the most frequently diagnosed cancer, contributing 11.7% of all new cases worldwide. Lung cancer, however, continues to lead in mortality, representing 18% of all cancer-related deaths (1). The increasing burden of cancer, driven by aging populations and lifestyle changes, underscores the urgent need for innovative approaches to its diagnosis, prognosis, and treatment.

A critical aspect of cancer research involves identifying molecular targets that can provide insights into tumor biology and serve as potential diagnostic or therapeutic tools. Circular RNAs (circRNAs), a class of endogenous noncoding RNAs characterized by their covalently closed-loop structures, have emerged as key players in the pathophysiology of various cancers (2). Among

Correspondence to: Bahauddeen M. Alrfaei
*King Abdullah International Medical Research Center (KAIMRC), King Saud Bin Abdulaziz University for Health Sciences (KSAU-HS), Ministry of National Guard, Health Affairs, Riyadh, Saudi Arabia.
Email: Bahauddeen1@gmail.com; rfaeib@ksau-hs.edu.sa
Full list of author information is available at the end of the article.
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these, circSMARCA5, derived from exons 15 and 16 of the SMARCA5 gene, has garnered attention for its multifaceted roles in tumorigenesis, metastasis, and therapeutic resistance. CircSMARCA5 demonstrates exceptional stability, tissue specificity, and resistance to exonuclease-mediated degradation, making it a promising candidate for clinical applications (3). Its ability to regulate gene expression through mechanisms such as acting as a miRNA sponge, influencing RNA splicing, and modulating its parental gene's activity further highlights its therapeutic potential. circSMARCA5 induces a sponging effect on miR-432, which upregulates PDCD10 levels in prostate cancer cells. In addition, through sponging miR-17-3p and miR-181b-5p, circSMARCA5 exerts tumor-suppressive effects in hepatocellular carcinoma by enhancing TIMP3 expression and consequently suppressing tumor growth and metastasis (4-6).

In breast cancer, circSMARCA5 has been implicated in modulating the DNA damage repair pathway, thereby influencing tumor progression and therapeutic response (7). Similarly, in nonsmall cell lung cancer (NSCLC), circSMARCA5 has been shown to suppress cell proliferation, migration, and invasion through the miR-19b-3p/HOXA9 axis, underscoring its tumor-suppressive properties (8). Furthermore, its differential expression across various cancer types suggests its potential as a robust diagnostic and prognostic biomarker. Clinical studies have correlated circSMARCA5 levels with tumor stage, lymph node metastasis, and patient survival, emphasizing its utility in stratifying patients for personalized therapies (5, 9).

The objective of this review is to critically analyze the current understanding of circSMARCA5's role in breast and lung cancers, focusing on its molecular mechanisms, involvement in cancer stem cell (CSC) regulation, and potential clinical applications. By synthesizing insights from recent studies, this paper aims to highlight circSMARCA5's significance in cancer biology and its prospective utility in advancing personalized medicine, which aligns with the precision oncology paradigm, where molecular profiling guides tailored interventions.

The circSMARCA5 could play a pivotal role in personalized medicine, particularly in cancer therapeutics. Its differential expression across tumor subtypes and ability to regulate key oncogenic pathways (e.g., via sponging miR-17-3p/miR-181b-5p to modulate TIMP3) may enable patient stratification for targeted therapies. For instance, high circSMARCA5 levels could identify patients likely to respond to TIMP3-dependent treatments or miRNA inhibitors, while low expressers might benefit from circRNA restoration strategies (4-6).

This review explores the broader implications of circSMARCA5 in tumorigenesis and therapeutic resistance, highlighting its mechanisms of action and potential to overcome treatment barriers. These insights position circSMARCA5 as both a promising diagnostic marker and therapeutic target in cancer, advancing our understanding of circRNAs in oncology.

Background

Understanding the intricate mechanisms of cancer progression and identifying molecular targets for its management requires a detailed exploration of underlying cellular and genetic factors. The SWItch/Sucrose Non-Fermentable chromatin remodeling (SWI/SNF) complex and its associated components, such as the SMARCA5 gene, have emerged as pivotal regulators of chromatin remodeling and gene expression. CircSMARCA5, a circRNA derived from this gene, plays a significant role in cancer biology, offering insights into tumorigenesis, metastasis, and therapeutic resistance. Notably, circSMARCA5 may act as a downstream effector or modulator of SWI/SNF-driven transcriptional programs, potentially bridging chromatin remodeling with post-transcriptional regulation. Additionally, CSCs represent a unique subset of cells that sustain tumor growth and contribute to therapy resistance. Intriguingly, circSMARCA5's ability to influence key signaling pathways (e.g., Wnt/β-catenin or Notch) aligns with its putative role in CSC maintenance, suggesting a functional triad between SWI/SNF dysfunction, circSMARCA5 activity, and CSC plasticity. This section explores the functional relevance of the SWI/SNF complex, the molecular characteristics of circSMARCA5, and the importance of CSCs in cancer progression.

Overview of the SWI/SNF complex and SMARCA5

The SWI/SNF complex, a multiprotein assembly, plays a critical role in chromatin remodeling by altering nucleosome positioning and histone-DNA interactions. This ATP-dependent mechanism facilitates the accessibility of transcriptional machinery to genomic DNA, thereby regulating essential cellular processes such as transcription, replication, and DNA repair (10). Dysfunction of the SWI/SNF complex is implicated in numerous diseases, including cancer, where it often acts as either a tumor suppressor or an oncogenic factor depending on the cellular context (11). As part of this complex, the SMARCA5 gene encodes the helicase hSNF2H, which exhibits both ATPase and helicase activities. These enzymatic functions are essential for maintaining chromatin stability and mediating nucleosome assembly.

SMARCA5 is located on chromosome 4q31.21 and encodes a protein involved in the regulation of chromatin architecture, which impacts cell proliferation and differentiation (4). This protein interacts with histone octamers, influencing higher order chromatin structure and enabling transcriptional regulation and DNA damage repair (12). SMARCA5 has been identified as a critical player in multiple oncogenic pathways, with its overexpression reported in gliomas, leukemia, and various epithelial cancers (10). Moreover, the epigenetic regulation of SMARCA5 by cancer-associated microRNAs has been shown to significantly impact tumor progression (11). This dynamic regulation underscores the importance of SMARCA5 in maintaining genomic integrity and its potential as a therapeutic target.

CircSMARCA5

CircSMARCA5 is a covalently closed circRNA produced by back-splicing of exons 15-16 of the SMARCA5 gene. Its unique loop structure, lacking free 5' and 3' ends, confers exceptional resistance to exonuclease degradation (13), resulting in a remarkable half-life exceeding 24 hours - far surpassing its linear transcript counterpart. CircSMARCA5 has a half-life exceeding 24 hours, significantly longer than the linear transcript of SMARCA5, making it a robust molecular entity for studying tumor biology (4). This exceptional stability enables cellular accumulation and sustained regulatory activity, making circSMARCA5 an especially valuable molecule for investigating tumor biology and gene expression control.

The biogenesis of circSMARCA5 is governed by intricate regulatory pathways involving both cis-regulatory elements and trans-acting factors. RNA-binding proteins (RBPs), such as DHX9 and QKI, play pivotal roles in its formation. While DHX9 suppresses circRNA synthesis by binding to complementary sequences flanking the pre-mRNA, QKI promotes exon circularization through intron interactions (7). These mechanisms highlight the tightly controlled nature of circSMARCA5 production, reflecting its physiological significance. Normally and functionally, circSMARCA5 acts as a miRNA sponge, regulating gene expression by sequestering microRNAs that would otherwise target specific mRNAs. When malignancy occurs, this sponging activity shows profound implications, where it modulates key signaling pathways involved in proliferation, migration, and invasion (6).

CircSMARCA5's stability and tissue-specific expression make it a promising biomarker for cancer diagnosis and prognosis. Studies have demonstrated its downregulation in breast and lung cancers, with overexpression experiments showing its potential to inhibit tumor growth and enhance chemosensitivity (8). This dual role as a regulator of gene expression and a biomarker underscores circSMARCA5's relevance in both fundamental research and clinical oncology.

Cancer stem cells (CSCs)

CSCs are a subset of tumor cells characterized by their ability to self-renew and differentiate into multiple lineages, akin to normal stem cells. These cells are believed to drive tumor initiation, progression, and recurrence, making them critical targets in cancer therapy. CSCs arise from either normal stem cells or through the reprogramming of differentiated tumor cells, acquiring stem-like properties (14). The plasticity of CSCs allows them to adapt to microenvironmental changes, contributing to their heterogeneity and resilience against conventional therapies (15).

A hallmark of CSCs is their reliance on specific signaling pathways for self-renewal and maintenance, such as Wnt, Notch, and Hedgehog pathways. These pathways, which are also active in normal stem cells, are often dysregulated in CSCs, leading to uncontrolled proliferation and survival (16). Additionally, CSCs exhibit enhanced motility and resistance to apoptosis, facilitating metastasis and therapeutic resistance. The identification of CSC-specific markers, such as CD44, CD24, and ALDH1, has enabled their isolation and characterization, providing insights into tumor biology and informing targeted therapeutic strategies (17).

CSCs differ from normal stem cells in their response to external stimuli and their propensity to form tumors. While normal stem cells contribute to tissue homeostasis, CSCs drive tumorigenesis by evading immune surveillance and exhibiting heightened resistance to chemotherapy and radiation (18). This resistance is attributed to their quiescent nature, efficient DNA repair mechanisms, and activation of survival pathways. Targeting CSCs requires a nuanced understanding of their unique biology, including their interactions with the tumor microenvironment and their role in promoting heterogeneity within the tumor mass.

CSCs have significant clinical implications, as they are often associated with poor prognosis and therapy resistance. Their ability to transition between mesenchymal and epithelial states enhances their invasive and metastatic potential (16). Understanding the molecular drivers of CSC behavior, including their reliance on circRNAs like circSMARCA5 for regulatory control, is essential for developing effective therapeutic interventions. The integration of CSC-targeting strategies with conventional therapies holds promise for improving cancer outcomes and reducing recurrence rates.

circSMARCA5 in cancer

circRNAs have emerged as a significant class of noncoding RNAs involved in the regulation of gene expression and tumorigenesis. Among these, circSMARCA5, derived from exons 15 and 16 of the SMARCA5 gene, has gained attention for its dual roles in cancer biology, functioning both as a tumor suppressor and as a modulator of cellular processes such as proliferation, migration, and DNA repair. Differential expression of circSMARCA5 has been observed in various cancers, notably breast cancer and NSCLC, underscoring its relevance in cancer progression and therapeutic targeting. This section delves into the roles of circSMARCA5 in breast and lung malignancies, with a focus on its functional implications, interactions with molecular pathways, and potential as a biomarker and therapeutic target.

Role in breast malignancy

Breast cancer, the most commonly diagnosed cancer in women globally, is a heterogeneous disease characterized by diverse molecular subtypes and complex pathophysiology. CircSMARCA5 has been identified as a key regulatory molecule in breast cancer progression, with its expression levels inversely correlated with tumor aggressiveness. Studies have shown that circSMARCA5 expression is significantly downregulated in breast cancer tissues and cell lines, suggesting its potential role as a tumor suppressor (7). Functionally, circSMARCA5 inhibits tumor growth by modulating DNA damage repair pathways and impairing chromatin remodeling.

It achieves this by interacting with its parental gene, SMARCA5, forming an R-loop—a three-stranded structure where the newly transcribed RNA binds to the DNA template, displacing the other DNA strand. This R-loop formation triggers a transcriptional pause at exon 15. This transcriptional regulation reduces the expression of linear SMARCA5, thereby limiting the tumor's capacity to repair DNA damage effectively (7).

The interplay between circSMARCA5 and SMARCA5 underscores the complexity of its role in breast cancer. While the linear form of SMARCA5 is associated with chromatin stability and transcriptional regulation, the circular form acts as a regulatory checkpoint, inhibiting the overactivation of these pathways. This balance is particularly critical in cancer cells, where DNA damage repair pathways are often hijacked to promote survival and resistance to therapy. By disrupting these processes, circSMARCA5 enhances the sensitivity of breast cancer cells to chemotherapeutic agents such as cisplatin (7). This chemosensitizing effect highlights the therapeutic potential of circSMARCA5 as a target for intervention in breast cancer.

Additionally, circSMARCA5 serves as a promising biomarker for breast cancer diagnosis and prognosis. Its expression levels have been linked to tumor stage, lymph node involvement, and patient survival outcomes (9). By integrating circSMARCA5 expression data into clinical workflows, oncologists could potentially improve risk stratification and treatment planning for breast cancer patients. Future research should focus on elucidating the precise molecular mechanisms underlying circSMARCA5's tumor-suppressive effects and developing strategies to restore its expression in breast cancer cells.

Role in lung malignancy

Lung cancer, comprising small cell lung cancer (SCLC) and NSCLC, is the leading cause of cancer-related mortality worldwide. CircSMARCA5 plays a pivotal role in NSCLC, where it is markedly downregulated in tumor tissues and cell lines. This downregulation correlates with increased tumor proliferation, migration, and invasion, emphasizing circSMARCA5's role as a tumor suppressor (8). Mechanistically, circSMARCA5 exerts its anti-tumor effects through the miR-19b-3p/HOXA9 pathway. By sponging miR-19b-3p, circSMARCA5 prevents the suppression of the HOXA9 gene, thereby restoring its tumor-suppressive functions. HOXA9 has been shown to counteract epithelial-mesenchymal transition (EMT), a process critical for metastasis, highlighting the significance of this regulatory axis in NSCLC progression (3).

The impact of circSMARCA5 on NSCLC extends beyond its molecular interactions. Clinically, its expression levels are strongly associated with key prognostic indicators such as tumor size, lymph node metastasis, TNM staging, and carcinoembryonic antigen (CEA) levels (9). These correlations suggest that circSMARCA5 could serve as an independent prognostic biomarker for lung cancer patients, aiding in the prediction of disease progression and treatment response. Furthermore, overexpression of circSMARCA5 in NSCLC cell lines has been shown to enhance chemosensitivity to agents such as gemcitabine and cisplatin, providing a potential avenue for improving therapeutic outcomes (8).

In contrast to NSCLC, the role of circSMARCA5 in SCLC remains less well-characterized. However, emerging evidence suggests that it may similarly influence pathways involved in tumor progression and therapy resistance. SCLC, characterized by high plasticity and rapid proliferation, is heavily reliant on CSCs for its aggressive behavior. Given circSMARCA5's regulatory roles in gene expression and stem cell-associated pathways, further investigation into its functions in SCLC could provide valuable insights into this challenging subtype (16).

The dual roles of circSMARCA5 as both a biomarker and a therapeutic target underscore its importance in lung cancer management. Restoring its expression in NSCLC and exploring its functions in SCLC could pave the way for novel therapeutic strategies. Additionally, integrating circSMARCA5 into diagnostic panels could enhance the accuracy of lung cancer detection and prognosis, ultimately improving patient outcomes.

Generally, CircSMARCA5 represents a critical molecular player in the pathophysiology of breast and lung cancers. Its ability to modulate DNA repair, influence key signaling pathways, and enhance chemosensitivity highlights its therapeutic potential. By bridging basic molecular insights with clinical applications, circSMARCA5 offers a promising avenue for advancing cancer diagnosis and treatment. Further research into its regulatory mechanisms and interactions will be essential for harnessing its full potential in oncology.

Molecular Mechanisms of circSMARCA5 in Tumorigenesis

The pathogenesis of cancer involves a multitude of complex molecular mechanisms, including the regulation of gene expression, signal transduction, and cellular homeostasis. CircRNAs, such as circSMARCA5, have emerged as critical players in these processes. As a stable, noncoding RNA derived from the SMARCA5 gene, circSMARCA5 is integral to various regulatory networks that influence tumorigenesis. These mechanisms can be categorized into upstream regulatory factors that control its production and downstream functions that mediate its effects on cancer progression. Understanding these pathways offers insights into their role as a tumor suppressor and a potential therapeutic target.

Upstream regulatory mechanisms

CircSMARCA5 biogenesis is tightly regulated by cis-elements and trans-factors like QKI. This RBP binds flanking introns of SMARCA5 pre-mRNA, bringing exons 15 and 16 together to enable back-splicing (Figure 1). QKI broadly promotes circRNA formation, and its dysregulation disrupts circSMARCA5 production, impairing its tumor-suppressive role (7).

In contrast, DHX9 suppresses circSMARCA5 by binding flanking introns and blocking back-splicing.

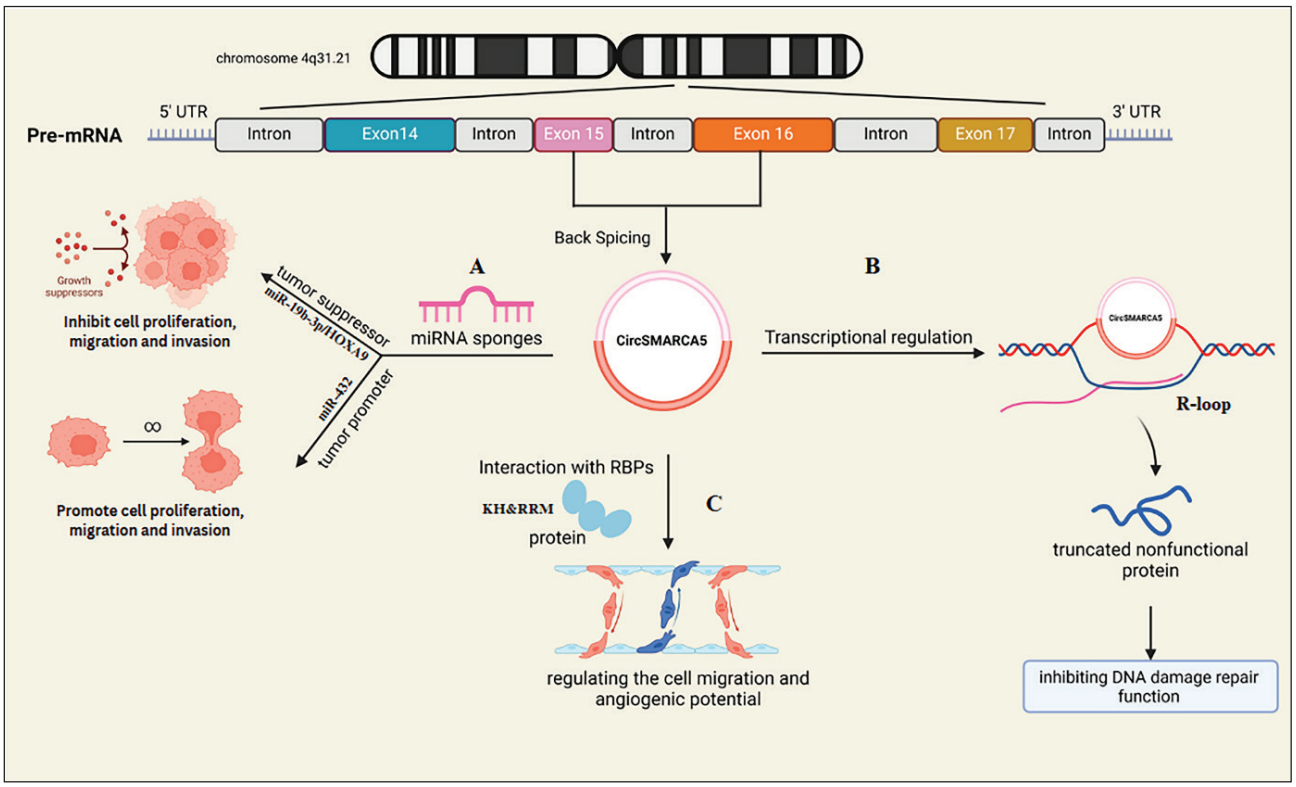

Figure 1. *CircSMARCA5 biogenesis and downstream regulatory pathways. With 464 nucleotides, CircSMARCA5 is derived from exons 15 and 16 of the SMARCA5 gene and is found on chromosome 4q31.21 (chr4:144464662-144465125). Biological functions of circSMARCA5. (A) CircSMARCA5 Acts as miRNA Sponges to Promote the Expression of Its Target Genes. (B) CircSMARCA5 Serves as a Transcriptional Regulator to Regulate Parental Gene Expression. (C) CircSMARCA5 Binds to RBP Involved in RNA Splicing Regulatory Process.*

Its overexpression reduces circSMARCA5, promoting oncogenesis. The opposing roles of QKI (promoter) and DHX9 (inhibitor) reveal a tightly balanced regulatory network—dysregulation in cancer disrupts this balance, lowering circSMARCA5 and driving tumor progression (3).

Upstream regulation of circSMARCA5 extends beyond RBPs to epigenetic mechanisms. For example, hypermethylation of the SMARCA5 promoter can silence transcription, reducing pre-mRNA substrate available for circSMARCA5 formation. Similarly, altered histone acetylation may compact chromatin, blocking access to back-splicing signals. Such dysregulation—frequent in cancer—depletes circSMARCA5, promoting tumor progression. Targeting these modifications (e.g., with demethylating agents) could restore circSMARCA5 as a therapeutic strategy.

Downstream mechanisms

CircSMARCA5 exerts its tumor-suppressive effects through several downstream mechanisms, primarily functioning as a microRNA (miRNA) sponge and influencing parental gene expression. Its ability to bind and sequester specific miRNAs plays a pivotal role in modulating gene expression networks that drive tumorigenesis, Table 1. For instance, circSMARCA5 has been shown to interact with miR-19b-3p, a miRNA involved in promoting cancer cell proliferation and migration. By sponging miR-19b-3p, circSMARCA5 prevents the downregulation of its target gene, HOXA9, which acts as a tumor suppressor in NSCLC. This interaction underscores the significance of circSMARCA5 in maintaining the balance of oncogenic and tumor-suppressive pathways (8).

In addition to miRNA sponging, circSMARCA5 regulates the expression of its parental gene, SMARCA5. This regulation is mediated through the formation of an R-loop structure, which induces a transcriptional pause in exon 15 of the SMARCA5 gene. This pause reduces the production of linear SMARCA5 mRNA, which is associated with DNA repair and chromatin remodeling activities. By limiting linear SMARCA5 expression, circSMARCA5 disrupts the cancer cell's ability to repair DNA damage, rendering it more susceptible to chemotherapy and other therapeutic interventions (19). Downregulation of circSMARCA5 in NSCLC promotes tumor proliferation, migration, and invasion by derepressing oncogenic miRNAs (e.g., miR-17-3p/miR-181b-5p), which subsequently target tumor-suppressive pathways (e.g., TIMP3), thereby enhancing extracellular matrix degradation and metastatic potential (20). The dual role of circSMARCA5 as a miRNA sponge and a transcriptional regulator highlights the multifaceted functions of circSMARCA5 in cancer biology, see Table 1.

Furthermore, circSMARCA5 interacts with other RBPs to influence RNA splicing and post-transcriptional regulation. These interactions form circRNA-protein

Table 1. *Summarizes the microRNAs affected by circSMARCA5 expression in various cancers.*

Cancer Types	MicroRNA	Reference
Multiple myeloma (MM)	miR-767-5p	(21)
Colon cancer	miR-552	(22)
NSCLC	miR-670-5p	(23)
Colorectal cancer	miR-39-3p	(24)
Prostate cancer	miR-181b-5p miR-17-3p	(20)
Bladder cancer	miR-432	(25)
Gastric cancer	miR-346/ FBXL2 axis	(26)
Glioblastoma multiforme	miR-126-3p, miR-515-5p	(27)
Nasopharyngeal carcinoma (NPC)	miR-582-3p	(28)
Cholangiocarcinoma	miR-95-3p	(29)

complexes that can modulate cellular processes such as proliferation, apoptosis, and metastasis. For example, circSMARCA5's binding to splicing factors has been implicated in altering the splicing patterns of oncogenes and tumor suppressors, contributing to its anti-tumor effects (4). These downstream mechanisms illustrate the broad scope of circSMARCA5's influence on cancer progression and its potential as a therapeutic target.

circSMARCA5 in Metastasis

Metastasis is the primary cause of cancer-related death, which is a hallmark of malignancy. Metastasis is the process by which cancer cells spread from the primary tumor to distant sites. CircSMARCA5 has been implicated in regulating key pathways that drive metastatic progression, making it a critical focus of cancer research. Its role in metastasis is multifaceted, encompassing its effects on cellular motility, EMT, and interactions with the tumor microenvironment.

Mechanistically, circSMARCA5 inhibits EMT, a process by which epithelial cells lose their polarity and adhesion properties to acquire a mesenchymal phenotype. EMT is essential for cancer cells to invade surrounding tissues and enter the circulatory system. In NSCLC, circSMARCA5 suppresses EMT by sponging miR-19b-3p, thereby upregulating HOXA9, a gene known to counteract EMT and reduce metastatic potential. This regulatory axis highlights circSMARCA5's role as a tumor suppressor in metastasis and underscores the therapeutic potential of restoring its expression in metastatic cancers (8).

Evidence from multiple cancer types further supports circSMARCA5's involvement in metastasis. In breast cancer, reduced levels of circSMARCA5 have been associated with increased lymph node metastasis and poorer clinical outcomes. Its ability to modulate DNA damage repair pathways and chromatin remodeling also impacts the metastatic potential of cancer cells, as these processes are crucial for maintaining genomic integrity during cell migration (7). These findings suggest that circSMARCA5 may serve as a biomarker for predicting metastatic risk and patient prognosis.

The influence of circSMARCA5 on metastasis extends to its interactions with the tumor microenvironment. By regulating the expression of genes involved in immune evasion and angiogenesis, circSMARCA5 modulates the interplay between cancer cells and their surrounding stromal and immune cells. This modulation can impact the ability of cancer cells to establish secondary tumors, making circSMARCA5 a target for therapies aimed at disrupting metastatic niches (3). Future research should explore the therapeutic implications of these findings, particularly in the context of combination therapies that integrate circSMARCA5-targeting agents with conventional treatments. Generally, circSMARCA5's regulatory roles in upstream and downstream pathways, as well as its impact on metastasis, position it as a key molecular target in cancer therapy. Its ability to modulate tumor progression through multiple mechanisms underscores its potential as a biomarker and a therapeutic agent, offering new avenues for combating cancer and improving patient outcomes.

Clinical Applications of circSMARCA5

The exploration of circRNAs as diagnostic, prognostic, and therapeutic tools has transformed the landscape of cancer research. CircSMARCA5, a circRNAs derived from the SMARCA5 gene, has shown remarkable promise in clinical oncology due to its stability, tissue-specific expression, and multifaceted regulatory roles. As a biomarker, circSMARCA5 demonstrates strong correlations with tumor progression and survival outcomes across various cancers, offering potential for personalized medicine. Furthermore, its ability to modulate DNA repair pathways and enhance chemosensitivity highlights its therapeutic potential. This section discusses the diagnostic and prognostic utility of circSMARCA5, followed by its application as a therapeutic target in cancer treatment.

Therapeutic target

Beyond its role as a biomarker, circSMARCA5 holds significant promise as a therapeutic target, particularly in cancers where its expression is diminished. The ability of circSMARCA5 to modulate critical cellular processes

such as DNA repair, proliferation, and metastasis provides a strong rationale for its therapeutic exploitation. Restoring circSMARCA5 expression in tumor cells or mimicking its functions through synthetic analogs could inhibit tumor growth and enhance chemosensitivity, paving the way for novel cancer treatments.

In breast cancer, circSMARCA5 has been shown to impair DNA repair mechanisms, sensitizing cancer cells to chemotherapeutic agents. Xu et al. (19) reported that circSMARCA5 inhibits the DNA damage repair capacity of breast cancer cells by downregulating linear SMARCA5 expression. This effect disrupts chromatin remodeling and increases susceptibility to cisplatin, a commonly used chemotherapy drug. The potential to amplify this chemosensitizing effect through circSMARCA5-based interventions could significantly improve treatment outcomes in breast cancer patients, particularly those with drug-resistant tumors.

Similarly, in NSCLC, circSMARCA5 overexpression has been associated with reduced cell proliferation, migration, and invasion. Its interaction with the miR-19b-3p/HOXA9 pathway further highlights its therapeutic relevance, as restoring this axis could suppress tumor progression and enhance the efficacy of conventional therapies (8). Studies have also shown that circSMARCA5 enhances chemosensitivity to gemcitabine and cisplatin in NSCLC cells, providing a compelling argument for its integration into combination therapy regimens (3).

The future of circSMARCA5-targeted therapies lies in the development of delivery systems that can effectively restore or mimic its function in cancer cells. RNA-based therapies, including circRNA mimics and small interfering RNAs (siRNAs) targeting pathways antagonistic to circSMARCA5, represent promising strategies. Additionally, advances in nanotechnology could facilitate the delivery of circSMARCA5-based therapeutics to tumor sites with high precision, minimizing off-target effects and maximizing therapeutic efficacy (4). Such innovations could revolutionize cancer treatment, particularly for malignancies with limited therapeutic options.

Overall, circSMARCA5's dual role as a diagnostic and prognostic biomarker, coupled with its therapeutic potential, positions it as a pivotal molecule in clinical oncology. Its ability to provide insights into tumor biology and enhance the efficacy of existing therapies highlights its transformative potential in cancer management. Future research should focus on overcoming challenges related to its clinical application, including delivery mechanisms and large-scale validation studies, to fully harness the benefits of circSMARCA5 in personalized medicine.

Diagnostic and prognostic biomarker

The identification of reliable biomarkers is a cornerstone of cancer diagnosis and prognosis, enabling early detection, risk stratification, and treatment monitoring. CircSMARCA5 has emerged as a significant biomarker due to its differential expression in tumors compared to normal tissues. Its stability in bodily fluids, resistance to RNase degradation, and tissue-specific expression make it a particularly attractive candidate for clinical applications (4). Numerous studies have highlighted its diagnostic and prognostic value in cancers such as breast, lung, gastric, and colorectal malignancies.

In breast cancer, reduced expression of circSMARCA5 correlates with advanced tumor stages, increased lymph node metastasis, and poor survival outcomes. Xue et al. (7) demonstrated that circSMARCA5 expression is inversely associated with tumor aggressiveness and resistance to therapy. Similarly, in lung cancer, especially NSCLC, circSMARCA5 levels have been linked to key prognostic indicators, including tumor size, TNM stage, and CEA levels. Studies suggest that patients with higher circSMARCA5 expression exhibit better disease-free and overall survival rates, emphasizing its role as a robust prognostic marker (8, 9).

The utility of circSMARCA5 as a biomarker extends beyond its diagnostic capabilities. In personalized medicine, circSMARCA5 can guide therapeutic decisions by stratifying patients based on their molecular profiles. For instance, its expression levels could predict the efficacy of DNA-damaging agents like cisplatin, enabling tailored treatment regimens. Moreover, its presence in extracellular vesicles and circulating tumor cells presents opportunities for noninvasive liquid biopsy (body fluids such as blood) approaches, offering a convenient method for real-time monitoring of tumor dynamics (5). These applications underscore the transformative potential of circSMARCA5 in precision oncology, where treatments are increasingly personalized to maximize efficacy and minimize adverse effects.

Significance of circSMARCA5 targeting

Current cancer therapies, including chemotherapy and targeted agents, often face limitations such as drug resistance, systemic toxicity, and inability to fully eradicate metastatic disease. circSMARCA5-targeted therapies could address these challenges by restoring tumor-suppressive circRNAs that modulates key oncogenic pathways. Since circSMARCA5 is frequently downregulated in cancers, its reactivation may enhance treatment efficacy, reduce resistance mechanisms, and provide a more tumor-specific approach with fewer off-target effects.

Conclusion

The current understanding of circSMARCA5's role in Breast and Lung Malignancy, particularly its crucial contribution to tumor development and potential clinical applications. CSCs, which have the ability to self-renew and can arise from normal stem cells, progenitor cells, or differentiated cancer cells, are a key focus. The prevailing theory suggests that malignancies are primarily driven by a small subset of highly tumorigenic cells (comprising less than 5% of the tumor cell population) with stem cell properties, referred to as CSCs. Researchers have also identified a significant inverse correlation between the expression of circSMARCA5 and its parent gene. A decrease in circSMARCA5 levels has been observed in both breast cancer and NSCLC tissues and cell lines. Furthermore, the molecular mechanisms

of circSMARCA5 encompass both upstream and downstream regulation. Consequently, the presence of circSMARCA5 can enhance cancer detection and serve as a valuable prognostic biomarker for patients. In the future, circSMARCA5 may serve as a promising target for therapeutic interventions in cancer treatment, offering new avenues for personalized medicine and novel strategies for cancer management.

Patient informed consent
Not necessary for this manuscript.

Ethics committee approval
Not necessary for this manuscript.

Conflict of interest
The authors declare that they have no conflict of interest regarding the publication of this article.

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Author details
Awjad Almotari[1,2], Bahauddeen M. Alrfaei[2,3], Amani A. Alghamedi[1], Abir A. Alamro[1]
1. Department of Biochemistry, College of Science, King Saud University, Riyadh, Saudi Arabia
2. King Abdullah International Medical Research Center (KAIMRC), King Saud Bin Abdulaziz University for Health Sciences (KSAU-HS), Ministry of National Guard, Health Affairs, Riyadh, Saudi Arabia
3. College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Ministry of National Guard-Health Affairs, Riyadh, Saudi Arabia

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