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CircSKA3 in Colorectal Cancer: Molecular Mechanisms, Therapeutic Potential, and Translational Challenges

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Abstract. Colorectal cancer (CRC) is one of the most common malignant tumors worldwide and is the second leading cause of cancer death globally. The current treatment of CRC encompasses surgical resection, chemotherapy, targeted therapy, and immunotherapy and the two main problems that need to be addressed are drug resistance and metastatic recurrence. Circular RNAs (circRNAs) is a newly discovered class of covalently closed non-coding RNAs that have been found to play important roles in regulation of gene expression and tumor biology in recent years. One of them, circSKA3 (hsa_circ_0000467), has been shown in pre-clinical studies to have oncogenic potential in CRC and multiple other cancers. CircSKA3 executes its mechanism through activating multiple pathways to promote tumor cell invasion, metastasis, and epithelial-mesenchymal transition (EMT). Clinical studies have shown that inhibiting circSKA3 with antisense oligonucleotides (ASOs), small interfering RNA (siRNA) and CRISPR-Cas13 systems completely reduces tumor growth. Therefore, circSKA3 association has high potential translational value despite some limitations of technical achievement such as efficient delivery, off-target effects, and corroboration with large clinical cohorts. This article provides a systematic overview of the molecular mechanisms of circSKA3, considers its role and potential as a biomarker and therapeutic target, and reviews the possibilities and challenges of developing circSKA3-based intervention strategies for the treatment of CRC.

Keywords: colorectal cancer, circSKA3, epithelial–mesenchymal transition, SLUG, E-cadherin

1. Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide. According to statistics, there were more than 1.9 million new CRC cases and about 900,000 deaths worldwide in 2020 [1]. Despite advances in surgery, chemotherapy, targeted therapy, and immunotherapy, the prognosis for patients with advanced CRC remains unsatisfactory, due to distant metastasis and the emergence of drug resistance. Among the many mechanisms that drive CRC development, epithelial-mesenchymal transition (EMT) is particularly critical [2]. EMT causes tumor cells to lose their epithelial cell characteristics and acquire a mesenchymal phenotype, resulting in more substantial migration and invasion capabilities. The transcription factor Snail Family Transcriptional Repressor 2 (SLUG) (SNAI2) is a key regulator of EMT, which disrupts cell-to-cell junctions by inhibiting the

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expression of the epithelial marker molecule E-cadherin, thereby promoting tumor invasion [3]. Therefore, restoring the function of E-cadherin or inhibiting SLUG is considered an important potential strategy to inhibit metastasis.

In recent years, circRNAs have been gradually recognized as key regulators of EMT and tumorigenesis and development. circRNAs are formed by back splicing of precursor mRNAs and have a stable covalent closed-loop structure, making them less susceptible to degradation by exonucleases. Functionally, circRNAs can participate in gene regulation in a variety of ways: they can be used as competitive endogenous RNAs (ceRNAs) to "sponge" microRNAs, and they can bind RNA-binding proteins to affect their activity and localization, and they can also regulate the transcription of parental genes [4]. Aberrant circRNA expression has been shown to be closely related to tumor occurrence, progression, and drug resistance, while circRNA's stability and tissue specificity make it an ideal candidate for therapeutic intervention.CircSKA3(hsa_circ_0000467) is derived from exon 4 of the SKA3 gene and is strongly associated with CRC progression in recent years [5]. Numerous studies have shown that circSKA3 is significantly highly expressed in CRC and a variety of other cancers, and is associated with advanced stage, more aggressiveness, and poorer survival outcomes. Mechanistic studies have demonstrated that circSKA3 promotes EMT and metastasis through the circSKA3–SLUG–E-cadherin axis, as it can upregulate SLUG and downregulate E-cadherin, thereby enhancing tumor cell plasticity [5]. In addition to EMT, circSKA3 promotes c-Myc translation and SLUG stability by "sponging" miR-1238, stabilizing oncogenic transcripts (e.g., STAT5A), and interacting with RNA-binding proteins such as eIF4A3 and FUS. These multifaceted roles make circSKA3 a central regulator of CRC progression.circSKA3 is considered a promising therapeutic target due to its unique reverse splicing ligation site, significant functional effects, and high expression in cancer tissue-specific. Inhibition strategies against circSKA3 include antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), and CRISPR-Cas13 systems, among others, which enable selective degradation of circSKA3. Combined with advanced delivery platforms such as lipid nanoparticles and colon-targeted oral preparations, it may further improve its clinical translation feasibility. This review will systematically summarize the research progress of circSKA3 in CRC, focusing on its biological functions and molecular mechanisms, evaluating its potential as a biomarker and therapeutic target, and exploring the opportunities and challenges of circRNA-targeted therapy in clinical practice.

2. Expression and clinical association of circSKA3

Colorectal cancer arises against a backdrop of typical driver mutations, such as APC loss, KRAS activation, and hyperactive Wnt/β-catenin signalling. These events create a permissive environment for malignant transformation. Simultaneously, it is pertinent to note that circRNA is a non-coding molecule that has recently emerged as a modulator of transcriptional and post-transcriptional programs under the radar [4]; circRNA represents a non-linear RNA, which has a stable structure and is resistant to degradation. CircSKA3 is significantly differentially expressed in colorectal cancer relative to adjacent normal mucosa and adenoma tissues [5,6], with increased expression correlating to higher stage of tumor, lymph node status and worse prognosis. In other words, the circSKA3 in a clinically relevant oncogene. Further, it was shown that circSKA3 correlates with tumor size, depth of invasion and involvement of lymph nodes, and suggests its value in future as a biomarker of disease progression [7]. Clinical studies indicate that patients with elevated levels of circSKA3 within their tumor correlate with shorter survival and recurrence, which suggest that detection of circSKA3 expression may be an important molecular feature of aggressive disease in human colorectal cancer, and prognostic indicator of survival. Most significantly, an elevated level

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of circSKA3 represents a relic of a by-product of global transcriptional dysregulation, and specific regulatory events that link barriers to its recognition with oncogenic signaling cascades [2]. Functional assays will uncover that downregulating levels of circSKA3 using antisense oligonucleotide-mediated depletion will result in reduced cell proliferation, migration, and invasion in vitro, which inhibited tumor growth in vivo [5]. Taken together, these findings center circSKA3 in its context of being a driver of malignant transformation.

3. The circSKA3–SLUG–E-cadherin axis and EMT

CircSKA3 plays a central role in modulating the epithelial-mesenchymal transition (EMT) by binding the transcription factor SLUG (SNAI2). SLUG is normally targeted for degradation through the ubiquitination pathway, so the interaction with circSKA3 limits this pathway and stabilizes SLUG protein [5]. Stabilized SLUG can interfere with the transcription of E-cadherin, an important adhesion molecule defining normal epithelial characteristics, and this regulation shifts adherents junction dynamics and promotes mesenchymal characteristics in the cell. Functional assays demonstrate that circSKA3 knockdown increases E-cadherin and reduces migratory capacity, whereas circSKA3 overexpression decreases E-cadherin and enhances invasiveness. In vivo mouse xenograft research confirmed that circSKA3 obstruction will decrease metastatic nodules and repair epithelial characteristics [5]. Immunofluorescence and Western blot assays further validated altered EMT marker expression following circSKA3 modulation. These observations indicate that circSKA3 regulates EMT by stabilizing SLUG and suppressing E-cadherin, thereby enhancing invasive potential.

Epithelial-mesenchymal transition (EMT) involves epithelial cells losing polarity and intercellular adhesion while acquiring mesenchymal traits that promote migration and invasion [3]. CircSKA3 plays a crucial role in mediating EMT, a process centrally regulated by the transcription factor SLUG (also known as SNAI2), which suppresses the expression of epithelial markers—particularly E-cadherin, a key component of adherents junctions [3]. The absence of E-cadherin disrupts epithelial integrity by impairing cell adhesion and promotes the acquisition of an invasive phenotype. Studies indicate that circSKA3 directly regulates this axis by interacting with SLUG's ubiquitination machinery, preventing its proteasomal degradation. Under normal conditions, SLUG undergoes proteasome-mediated degradation, limiting its stability and restricting EMT activation. CircSKA3 interferes with this ubiquitin-dependent turnover, leading to SLUG protein accumulation [5]. Stable SLUG imposes stronger transcriptional repression on the CDH1 gene encoding E-cadherin, thereby weakening epithelial adhesion, and promoting mesenchymal transformation. Functionally, this regulatory cascade links high circSKA3 expression to enhanced migration and invasive capacity in cancer cells.

Experimental knockdown of circSKA3 restores ubiquitin-mediated SLUG degradation, rescues E-cadherin expression, and re-epithelializes cells [5]. This consequently reduces in vitro invasive potential and limits metastatic dissemination in vivo. The circSKA3-SLUG-E-cadherin axis process illustrates how circular RNAs exert stabilizing effects at the post-translational level to stabilize oncogenic transcription factors. It highlights a specific node where therapeutic interference could suppress EMT-driven progression while preserving broader cellular networks. By selectively targeting this interaction, circSKA3 inhibition may represent a novel therapeutic approach to block early metastatic events without broadly impairing essential developmental EMT.

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4. Protein interaction networks and translational control

Eukaryotic initiation factor 4A3 (eIF4A3) is a protein belonging to the eukaryotic translation initiation factor family. As an RNA helicase, it unravels RNA secondary structure. As a core component of the exosome complex, it coordinates mRNA quality control through nonsense-mediated decay and facilitates efficient protein translation initiation, preventing erroneous mRNAs from entering the translation process [6]. As part of the RNA quality control pathway, it degrades abnormal mRNAs containing premature stop codons, preventing the production of harmful truncated proteins. As an ATP-dependent RNA helicase, it remodels secondary structures within messenger RNA, facilitating ribosomal scanning and efficient protein synthesis. Abnormal eIF4A3 activity is associated with oncogenic translation programs, particularly by stabilizing and enhancing the translation of transcripts encoding growth regulators. As circSKA3 directly binds with eIF4A3, forming a ribonucleoprotein complex that enhances c-Myc mRNA translation [6]. The oncogenic transcription factor c-Myc is a key regulator of metabolic reprogramming, cellular proliferation, and tumor progression. By promoting eIF4A3 recruitment to c-Myc transcripts, circSKA3 enhances ribosome binding and accelerates protein synthesis. This selective enhancement of c-Myc translation keeps downstream pathways constantly active. These include glycolysis, nucleotide biosynthesis, and cell cycle regulation. Transcript levels remain unchanged, but functional studies show a clear effect. When circSKA3 is silenced, its interaction with eIF4A3 is disrupted, and c-Myc protein levels fall [6].

The data suggest that circSKA3 primarily operates at the translational level, adding post-transcriptional regulation to oncogenic signaling. Notwithstanding, the convergence of SLUG and c-Myc regulation by circSKA3 places this circular RNA as a hub which integrates invasion and proliferation programs. To upgrade the maintenance of the metabolic and proliferative requirements defined by an invasive tumor phenotype, SLUG facilitates an ability to stabilize epithelial-mesenchymal transition. From a therapeutic perspective, targeting circSKA3 not only destabilizes SLUG, but also stops the translation of c-Myc directly, thereby inhibiting invasion and proliferation. This dual influence shows that disrupting circRNAs as non-coding oncogenic hubs will have beneficial therapeutic outcomes over targeting one of the proteins.

5. MicroRNA sponge and epigenetic regulation

One of the most well-established purposes of circRNAs is as competitive endogenous RNAs that can sequester microRNAs, thereby releasing inhibition on downstream targets. CircSKA3 acts as a molecular sponge for miR-1238, a microRNA with context-dependent tumor-suppressing activity [7]. By physically binding to miR-1238, circSKA3 prevents its inhibitory effect on the mRNA encoding the m6A-reading protein YTHDF2. YTHDF2 belongs to the YTH domain protein family, which specifically recognizes m6A-methylated transcripts. In general, YTHDF2 encourages mRNA degradation by binding to methylated sites, thereby shaping the transcriptome and ensuring rapid turnover of unstable information. However, when circSKA3 sequesters miR1238, YTHDF2 expression is upregulated. STAT5A, which is a transcription factor belonging to the STAT family, combines cytokine and growth factor signaling. The subsequent increase in YTHDF2 changes the stability of the targets that have been selected, including STAT5A mRNA. In this situation, YTHDF2 interacts with methylated STAT5A transcripts to upgrade the stability and is unable to promote degradation; therefore, the level of steady-state protein will be elevated [7]. This increased stability and translation sustain and regulate downstream pathways governing cell proliferation, resistance to cell death, and metabolic reprogramming. Such abnormal stability effectively confers growth

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advantages and survival benefits to malignant cells. More importantly, the circSKA3-miR1238-YTHDF2-STAT5A axis demonstrates how a single circRNA can alter the epigenome through combining microRNA sponge capability and its interaction with regulation of readers/modifiers of RNA modification. From a therapeutic point of view, in the first instance, to disrupt circSKA3 expression directly, will effectively deactivate miR1238 which will reduce YTHDF2 upregulation. Or we can deliver synthetic copies of miR1238 (to avoid the circSKA3 binding so that inhibition returns to YTHDF2) or degrade circSKA3. Interventions fine-tuning in therapy is important - to avoid too much of a change to whole RNA degradation pathways while trying to maintain inhibition on STAT5A upregulation (again YTHDF2 can stabilize). But either way, fine-tuning will be important for any of the approaches, as they will need to avoid disrupting global RNA degradation pathways. Additionally, as the anti-splicing junction sequences directly pertain to circSKA3, it is an easy target for natural degradation using antisense oligonucleotides or CRISPR-Cas13 [7].

6. Signaling pathways and invasion biology

In addition to its function in EMT regulation and translational control, circSKA3 engages in signaling pathways that lead to invasion and metastasis. An extensive, well-researched pathway is the Wnt/β-catenin axis. It is frequently active in epithelial cancers; therefore, stabilizes stem-like characteristics, some invasive behavior, and therapy resistance [2]. In colorectal cancer, circSKA3 may contribute to Wnt signaling. It acts to promote the already hyperactive signaling cascade of Wnt/β- catenin functions, frequently regulated by APC mutations. Consequently, circSKA3 promotes the stabilization and nuclear accumulation of β-catenin. Ultimately promoting the transcription of the Wnt-responsive genes that regulate proliferation, epithelial–mesenchymal transition, and stemness [8-10]. The transcriptional program extends to cell cycle progression, epithelial plasticity, and remodels the extracellular matrix. Although these effects are oncogenic, they also create a therapeutic vulnerability. Reducing circSKA3 expression could lower β-catenin signaling output and compromise the adaptability of cancer cells.

Evidence from other tumor models suggests an additional mechanism. CircSKA3 interacts with the integrin/Tks5 complex to remodel the cytoskeleton and form invasive protrusions. These structures allow tumor cells to degrade extracellular matrix components and breach matrix barriers, providing a clear explanation for the enhanced invasiveness seen with circSKA3 upregulation [6]. While direct evidence in colorectal cancer is still emerging, cross-cancer findings suggest that circSKA3 integrates cytoskeletal remodeling with adhesion signalling.

Together, these pathways converge to position circSKA3 as a nodal regulator of invasion biology. Therapeutically, targeting circSKA3 could block multiple malignant hallmarks at once—limiting both proliferations driven by Wnt signaling and invasiveness mediated by cytoskeletal dynamics. Because circRNAs often display tissue- and disease-specific expression, circSKA3 represents an upstream target that could disrupt transcriptional and structural remodeling programs with high specificity [2,6].

7. Therapeutic targeting of circSKA3

There are multiple strategies that can be explored for circSKA3 therapeutics. One significant advantage of circRNAs is the covalently closed back-splicing junction. This structure is absent in linear transcripts and creates a unique feature for selective targeting. Researchers can design antisense oligonucleotides or small interfering RNAs that bind precisely to this junction. These molecules degrade the circular isoform of SKA3 while leaving the linear mRNA intact [8]. By

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exploiting this design, circSKA3 activity can be reduced without harming essential linear transcripts.

Clinical evidence indicates the feasibility of these types of approaches. RNA interference therapies have already been approved, such as Patisiran for hereditary transthyretin amyloidosis, which also shows that siRNA-based approaches can be safe and effective in patients [9]. Likewise, siRNA duplexes targeting the circSKA3 back-splicing junction have been able to disrupt the oncogenic functions of circSKA3, including EMT induction, promotion of translational activation, and the Wnt signaling pathway.

Another potential technology could be CRISPR–Cas13. Cas13 cleaves RNA, whereas Cas9 edits DNA. The system could be engineered to cleave circSKA3 specifically at the post-splicing junction. There is also a level of flexibility in designing the guide RNA, which makes Cas13 an interesting experimental and potential therapeutic agent [6].

CircSKA3 is not a single-pathway regulator. It influences the SLUG–E-cadherin axis, c-Myc translation, and the miR-1238/YTHDF2/STAT5A signaling cascade. This broad activity means that inhibiting circSKA3 has the potential to suppress multiple oncogenic programs at once, while also offering tissue selectivity.

8. Drug delivery pathways and mechanistic considerations

The successful delivery of circSKA3-targeting therapies requires methods that can carry nucleic acids into cancer cells while limiting systemic toxicity. As shown in table 1, there are three different methods.

One option is lipid nanoparticles (LNPs). These particles are built from synthetic lipid bilayers that encapsulate therapeutic oligonucleotides or CRISPR–Cas13 components. They protect the cargo from nuclease degradation and promote endosomal escape after uptake [11]. The power of this system has been proven by the success of mRNA vaccines. LNPs are efficient in encapsulation and scalable for production. However, they tend to accumulate in the liver and are quickly cleared by the reticuloendothelial system. This can cause off-target exposure and dose-related toxicity.

A second option is extracellular vehicles (EVs), especially exosomes. These natural nanovesicles mediate cell-to-cell communication. When engineered, they can carry circSKA3-targeting RNA. EVs show strong biocompatibility, low immunogenicity, and can cross biological barriers [12]. Still, challenges remain. Large-scale isolation is difficult, drug loading is often inconsistent, and the natural heterogeneity of EVs makes reproducibility hard to achieve.

A third approach involves viral vectors. Adeno-associated virus (AAV) is the most widely used system. It can deliver shRNA or CRISPR constructs that silence circSKA3 with high efficiency [13]. AAV also enables long-term expression of therapeutic sequences, making it suitable for sustained knockdown. Yet, viral delivery faces clear obstacles. These include immune responses, risks of insertional mutagenesis, and heavy regulatory barriers. Together, these factors currently limit its application in circRNA therapeutics.

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Table 1. Delivery platforms for circSKA3-targeting therapeutics [11-13]

Delivery system	Mechanism of action	Advantages	Limitations
Lipid Nanoparticles (LNPs)	Encapsulate siRNA/ASO or CRISPR components to promote endosomal release	Clinically validated, scalable, and prevents degradation	Liver accumulation, rapid clearance, systemic toxicity
Extracellular vesicles (EVs)	Naturally occurring vesicles are engineered to carry therapeutic RNA	High biocompatibility, low immunogenicity, and barrier-crossing capability	Challenges in large-scale isolation, population heterogeneity, and variable payloads
Adeno-associated virus (AAV)	Sustained expression of RNAi or Cas13 systems via viral delivery	Highly efficient, durable knockdown	Immunogenicity, insertion mutagenesis risk, regulatory hurdles

9. Discussion

Numerous research suggests that circSKA3 drives malignant behavior and performs as a therapeutic target. However, still have many critical limitations that must be considered before translating these findings into clinical practice. These limitations exist at multiple levels, including experimental design, biological interpretation, delivery technologies, and clinical application. Addressing these challenges is essential for realizing the therapeutic potential of circSKA3 functions.

9.1. Limitations of current experimental evidence

Currently, the majority of circSKA3 research depends on in vitro assays that use already established colorectal cancer cell lines or small-scale xenograft models. Even these models can provide critical mechanistic insights, but still not able to fully replicate the heterogeneity of human tumors. For instance, the variation of circRNA expression regulatory networks among different patients may affect the function of circSKA3, but these characteristics have not been systematically characterized [4]. The data sources from patients for analysis remain limited, with poor clinical follow-up. This increases the risk of sampling bias and reduces the likelihood of obtaining accurate data regarding circSKA3 as a prognostic or therapeutic response biomarker. Furthermore, functional validation has primarily focused on downstream pathways, leaving open the possibility of other uncharacterized interactions involving circSKA3. To address these issues, strategies are provided that expand analyses to large, multicenter patient cohorts with standardized clinical annotations, and from a biological aspect, integrating transcriptomics, proteomics, and epigenetics can provide a more comprehensive view of the purposes of circSKA3 [5]. To clarify the type of specific cells expression patterns and identify the heterogeneity of circSKA3 regulated, single-cell RNA sequencing can be used to provide cellular-level resolution.

9.2. Technical and methodological challenges

Current tools for silencing circSKA3, such as siRNA and antisense oligonucleotides, still face challenges. They often carry the risk of off-target activity. The similarity between circRNA junctions and linear mRNA makes reagent design difficult. In addition, the lack of standardized detection protocols limits reproducibility [4]. One solution is to combine different silencing strategies. Using siRNA, antisense oligonucleotides, and CRISPR–Cas13 together may increase specificity. At the same time, computational pipelines for circRNA identification need standardization. Junction

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sequences should always be confirmed by experimental validation. Chemical modifications offer another improvement. For example, 2′-O-methylation or phosphorothioate backbones can make oligonucleotides more stable and more specific. These modifications also reduce immunogenicity [6]. Such approaches have already improved siRNA therapies in other diseases and may be applied to circSKA3-targeting molecules.

9.3. Delivery barriers

A major limitation of circSKA3 therapy is delivering RNA-based inhibitors to tumor cells and ensuring their successful action within cellular pathways. Naked oligonucleotides are unstable in circulation and exhibit poor tumor penetration. Lipid nanoparticles (LNPs) have been widely used for RNA delivery and validated in mRNA vaccines awaiting clinical implementation, but concerns exist regarding systemic toxicity in colorectal cancer due to their accumulation in the liver [11]. Extracellular vehicles (EVs) have intrinsic targeting properties that can function as a biocompatible alternative, but low yield and payload capacity as their scalability restriction [12]. AAV vectors enable the long-term expression of antisense RNA but have limitations, including immunogenicity, insertion mutagenesis risks, and regulatory hurdles [13]. To improve these delivery methods, the first way is engineering LNPs for colon-targeted delivery, which could reduce hepatic accumulation. Another method is modifying EVs with surface ligands, which could enhance tumor tropism. Finally, scaling EV production could progressively address yield issues [13]. Local administration routes, such as rectal delivery or hydrogel-based carriers, offer additional specificity for colorectal tumors. These strategies underscore the importance of tailoring delivery methods to the disease context.

9.4. Safety concerns

Since circSKA3 regulates multiple downstream pathways, there is a risk that inhibition could produce unintended side effects in normal tissues. For example, excessive suppression of c-Myc translation may impair proliferation in healthy intestinal epithelium, while disruption of YTHDF2 activity could affect physiological RNA metabolic turnover. Furthermore, RNA-based therapeutics may trigger innate immune sensors, leading to inflammatory responses [5,6]. To mitigate these risks, oligonucleotides and incorporated chemical modifications must be designed to minimize immune activation [6]. Tissue-specific delivery systems, particularly those optimized for colorectal targeting, can reduce off-target exposure. Establishing multiple animal models for preclinical toxicology studies is essential to validate safety as a therapeutic approach.

9.5. Future development

Future progress in circSKA3 research will depend on biological validation and innovative therapeutic strategies. Biologically, circSKA3 should be evaluated as a predictive biomarker in larger patient cohorts, with attention to its potential role in treatment resistance and recurrence. Therapeutically, the development of colon-targeted nanoparticles and engineered EVs is crucial for achieving precise delivery [7]. Combination therapies may offer sustained clinical benefits. CircSKA3 inhibition could sensitize tumors to chemotherapy by reversing resistance or enhance immunotherapy by restoring epithelial adhesion and promoting immune infiltration. These hypotheses remain to be validated but represent future directions for preclinical testing. CircRNAs are characterized by stability, specificity, and unique antisense binding capabilities enabling

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selective inhibition [4]. However, as noted in reviews of RNA therapeutics, off-target effects, immune activation, and delivery remain prevalent obstacles [5,6]. Lessons learned from circSKA3, particularly regarding delivery and safety assessment, will also inform strategies for other circRNA targets. The development of nanoparticle-based circRNA therapies underscores the urgent need for these molecules, which may soon constitute a new class of precision oncology tools [7].

10. Conclusion

CircSKA3 has emerged as a significant and central regulator of malignant progression, as it integrates transcriptional, translational, and epigenomic networks. What is exceptional about circSKA3 is that while many circRNAs have been implicated in limited roles, circSKA3 is capable of stabilizing oncogenic transcription factors and increasing translation of proliferation inducers, as well as regulating RNA modification readers. CircSKA3 is highly upregulated in colorectal cancer. Notably, circSKA3 expression is associated with advanced disease that correlates with survival. Findings support the emerging role of circSKA3 as a biomarker of aggressive disease and therapeutic target. The unique circular back-splicing junction of circSKA3 presents various opportunities for selective inhibition. Specifically, antisense oligonucleotides, siRNAs, and CRISPR–Cas13 can be applied to lower the specificity of targeting the circSKA3 back-splice junction. Our preclinical studies have consistently demonstrated the effects of silencing circSKA3 on proliferation, invasion, and metastasis; thus, implicating circSKA3 as a druggable target. Clinical advances in RNA interference drugs add significant value to our findings. In addition, existing siRNA therapies in other diseases demonstrate circSKA3-based interventions are feasible in practice. Nevertheless, several important issues must first be addressed. Clinical trial validation in similar patient cohorts is still in its infancy. Detection methods for circRNA vary from study to study. Off-target risks associated with nucleic acid-based strategies remain a consideration. Delivery of nucleic acid therapeutic agents is still and will remain a considerable challenge. To address these issues will require broadening the strategy. For example, multi-omics studies can be conducted to further elucidate the active role circSKA3 plays in invasion and metastasis in detail. In addition, large-scale colon cancer clinical cohorts are also still required to unequivocally validate the prognostic utility and therapeutic value of circSKA3. There are other avenues we need to explore too, for example colon targeted delivery using engineered nanoparticles or extracellular vesicles. Future investigations should also explore treating combining circSKA3 inhibition with other treatment modalities, such as restoration of epithelial adhesion or inhibition of proliferation to improve responses to chemotherapy, immunotherapy, and alternative treatment modalities. Combined, this study establishes circSKA3 as a therapeutic example for circRNA and represents a systematic approach to developing second-generation RNA-based therapeutic strategies in precision oncology.

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