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The Role of microRNA-31 in the Initiation and rogression of Colorectal Cancer

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ABSTRACT

miR-31 is critically involved in the initiation and progression of CRC by regulating multiple pathways essential for tumorigenesis and influencing various cellular functions, such as proliferation, apoptosis, epithelial-mesenchymal transition (EMT), metastasis, and chemoresistance. miR-31 also impacts EMT-related transcription factors such as ZEB1, SNAIL, and TWIST, which further facilitate the shift to a mesenchymal state, leading to increased invasiveness and metastatic spread of CRC cells, commonly to organs like the liver, which worsens patient prognosis in the context of apoptosis, miR-31 inhibits pro-apoptotic factors such as BAX and Caspase-3, reducing programmed cell death and allowing cancer cells to survive longer this anti-apoptotic influence is essential for miR-31's role in chemoresistance, as it enables cancer cells to evade the cytotoxic effects of chemotherapy. Interestingly, despite its primarily oncogenic role, miR-31 has shown context-dependent tumor-suppressive properties in specific genetic or environmental conditions under certain conditions, miR-31 may target oncogenes or reduce the activity of tumor-promoting pathways, although these instances are relatively rare and context-specific, influenced by factors like genetic mutations clinically, miR-31's expression level is correlated with CRC stage, metastatic capacity, and patient prognosis, indicating its potential utility as a biomarker for risk assessment and prognosis. Elevated miR-31 levels are associated with advanced CRC stages, increased tumor aggressiveness, and poor overall survival, underscoring its relevance in patient management ongoing research is investigating miR-31 inhibitors as a therapeutic option to counteract its oncogenic effects and improve treatment responses by sensitizing CRC cells to chemotherapeutic-induced apoptosis.

Keywords: Biogenesis, Colorectal Cancer, EMT, Mir-31

INTRODUCTION:

MicroRNA-31 (miR-31) has emerged as a critical regulator in the onset and progression of colorectal cancer (CRC), a leading cause of cancer-related mortality worldwide. As a small, non-coding RNA molecule, miR-31 plays a multifaceted role in cellular processes that are essential for tumorigenesis, including cell proliferation, apoptosis, invasion, and metastasis (1, 2). Its dysregulation has been implicated in various aspects of CRC pathophysiology, highlighting its potential as both a biomarker and therapeutic target (3, 4).

The biogenesis and functional mechanisms of miR-31 are influenced by numerous oncogenic pathways, including the Wnt/β-catenin, PI3K/AKT/mTOR, and MAPK signaling pathways (5, 6). By modulating key molecular targets within these pathways, miR-31 can promote cancer cell survival and facilitate the epithelial-mesenchymal transition (EMT), a critical process that enables cancer cells to acquire invasive properties. Moreover, miR-31 has been associated with chemoresistance, allowing CRC cells to evade apoptosis and thrive in the presence of therapeutic agents (1, 3).

Understanding the roles of miR-31 in CRC provides essential insights into the molecular underpinnings of the disease and underscores its potential as a prognostic biomarker. Elevated levels of miR-31 have been linked to advanced disease stages and poor clinical outcomes, suggesting its utility in risk stratification and therapeutic decision-making (2, 4). Consequently, ongoing research into miR-31's function may not only illuminate the complex biology of colorectal cancer but also pave the way for innovative diagnostic and therapeutic strategies aimed at improving patient prognosis and treatment efficacy (5, 6).

Colorectal cancer

Cancer is the most common disease in the world, and CRC is the third most deadly cancer in the world (7). Several studies have revealed that CRC is the third most deadly cancer worldwide (8). There is substantial evidence suggesting that CRC mortality and morbidity could be mitigated in regions such as Europe and North America (9). Since CRC typically takes 10 to 15 years to develop, early detection of precancerous polyps before malignant transformation is essential for routine screening (10). Numerous factors contribute to the initiation and progression of CRC (11). Genetics plays a critical role in the onset and progression of all cancers, including CRC (6). CRC arises from genetic mutations and alterations in protein expression that drive cancer initiation, progression, and invasion. Other factors, such as miRNAs, have also been implicated in CRC progression and suppression (12). Early detection of CRC has the potential to reduce CRC-related mortality. However, despite advances in diagnostic techniques, many CRC cases are diagnosed at advanced stages (6). Understanding the molecular mechanisms underlying CRC pathogenesis is critical to addressing this challenge (6). These mechanisms often involve mutations in critical genes, abnormal DNA methylation patterns, and dysregulated miRNA expression (13). Therefore, this review aims to elucidate the oncogenic and anti-cancer functions of different types of miRNA in CRC (14).

miRNA structure and biogenesis

miRNA can control at least 30% of the genes that encode proteins, representing between 1 and 5% of the human genome (15). The human genome contains approximately 940 different miRNA molecules that have been identified to date (16). Although much remains to be understood about the precise targets and biological roles of miRNA molecules; it is clear that miRNA is essential for regulating gene expression, which controls various cellular and metabolic processes (17). MiRNAs are single-stranded, non-coding, tiny, evolutionarily conserved RNA molecules that bind to target miRNA through one of two different ways to prevent the formation of proteins (14). Primary miRNA (pri-miRNA) is cleaved twice to produce mature miRNA, which then joins the effector complex known as the RNA induced silencing complex (RISC) (18). By base-pairing with the target mRNA, the miRNA acts as a guide to negatively inhibit the expression of the target mRNA (2). The silencing method used, either translation inhibition or target messenger RNA (mRNA) cleavage followed by destruction, depends on the complementarity of the guide and the target mRNA (14). While the general function of miRNA is understood, the molecular aspects of miRNA synthesis and genes silencing remain unknown (5). Examining the expression profiles of these molecules provides information on their regulation and function, even though the biological role of the detected miRNAs may not be understood (6). These findings suggest that miRNA expression profiles are altered in particular tumors, suggesting a potential role for miRNA in the etiology of cancer and other diseases (19). Despite our poor understanding of these molecules, baseline

expression profiling is clinically relevant to cancer diagnosis, progression, and outcome (14).

MicroRNA-31 functions

miR-31 is critically involved in the initiation and progression of CRC by regulating multiple pathways essential for tumorigenesis and influencing various cellular functions, such as proliferation, apoptosis, epithelial-mesenchymal transition (EMT), metastasis, and chemoresistance. Acting primarily as an oncogene, miR-31 enhances CRC cell survival and aggressiveness by modulating key pathways firstly, miR-31 activates the Wnt/β-catenin signaling pathway, a fundamental pathway in CRC development, by targeting inhibitors such as AXIN2 and GSK3β, crucial components in β-catenin degradation. By downregulating these negative regulators, miR-31 stabilizes β-catenin, which accumulates in the nucleus and promotes transcriptional activity through TCF/LEF transcription factors. This activity triggers the expression of genes like CCND1 (cyclin D1) and MYC, supporting enhanced CRC cell proliferation, stemness, and tumor-initiating capacity (15, 16).

Furthermore, miR-31 modulates the Ras/Raf/MEK/ERK (MAPK) pathway by inhibiting RASA1 and SPRY2, which are responsible for regulating Ras activity. With these suppressors downregulated, miR-31 sustains Ras signaling, promoting a continuous cascade through Raf, MEK, and ERK, leading to oncogenic transcriptional activities via factors like ELK1 and AP-1. This sustained activation is closely associated with increased tumor progression and invasiveness, resulting in a more aggressive CRC phenotype the PI3K/AKT/mTOR pathway, another critical axis in CRC, is also influenced by miR-31 by targeting PTEN, a key tumor suppressor and negative regulator of this pathway, miR-31 amplifies PI3K/AKT signaling, resulting in AKT activation and subsequent mTOR upregulation. This pathway is linked to enhanced protein synthesis, cellular growth, and metabolic reprogramming, which benefit CRC cells in hostile environments, including under chemotherapeutic stress consequently, miR-31 also supports chemoresistance by inhibiting apoptosis, which allows CRC cells to withstand agents like 5-fluorouracil (5-FU) and oxaliplatin, frequently used in CRC treatment (1, 2, 3, 17, 18).

In addition, miR-31 plays a crucial role in promoting EMT, a process by which epithelial cells acquire a mesenchymal phenotype, gaining increased motility and invasiveness. This transition is critical for metastasis. miR-31 downregulates E-cadherin (an epithelial marker) and upregulates mesenchymal markers like N-cadherin and vimentin. miR-31 also impacts EMT-related transcription factors such as ZEB1, SNAIL, and TWIST, which further facilitate the shift to a mesenchymal state, leading to increased invasiveness and metastatic spread of CRC cells, commonly to organs like the liver, which worsens patient prognosis in the context of apoptosis, miR-31 inhibits pro-apoptotic factors such as BAX and Caspase-3, reducing programmed cell death and allowing cancer cells to survive longer this anti-apoptotic influence is essential for miR-31's role in chemoresistance, as it enables cancer cells to evade the cytotoxic effects of chemotherapy. miR-31 also upregulates anti-apoptotic proteins like Bcl-2 and MCL1, further promoting survival and chemoresistance (2, 18, 19).

Interestingly, despite its primarily oncogenic role, miR-31 has shown context-dependent tumor-suppressive properties in specific genetic or environmental conditions under certain conditions, miR-31 may target oncogenes or reduce the activity of tumor-promoting pathways, although these instances are relatively rare and context-specific, influenced by factors like genetic mutations clinically, miR-31's expression level is correlated with CRC stage, metastatic capacity, and patient prognosis, indicating its potential utility as a biomarker for risk assessment and prognosis. Elevated miR-31 levels are associated with advanced CRC stages, increased tumor aggressiveness, and poor overall survival, underscoring its relevance in patient management ongoing research is investigating miR-31 inhibitors as a therapeutic option to counteract its oncogenic effects and improve treatment responses by sensitizing CRC cells to chemotherapeutic-induced apoptosis. As such, miR-31 is not only a significant contributor to CRC pathophysiology but also holds promise for developing more effective treatment strategies and personalized therapeutic approaches for CRC patients (4, 5, 6, 16, 20, 21).

Biogenesis of miR-31 in Colorectal Cancer Cell Lines

miR-31 is a well-characterized microRNA that has emerged as a significant player in the pathogenesis of CRC. Its biogenesis involves a complex series of steps that dictate its expression and function within CRC cell lines (2, 3, 6, 22). Understanding these processes is crucial, as miR-31 acts primarily as an oncogene, contributing to tumor growth, invasion, and metastasis (23).

The biogenesis of miR-31 begins with its transcription

from the genomic locus located in the MMP2 gene. This transcription is primarily facilitated by RNA polymerase II, which synthesizes a long primary transcript known as pri-miR-31. This pri-miRNA is characterized by a stem-loop structure that is essential for subsequent processing. The expression of pri-miR-31 is regulated by various oncogenic signals, including the Wnt/β-catenin signaling pathway. In CRC, the activation of β-catenin promotes the transcription of miR-31 through interactions with TCF/LEF transcription factors, leading to increased levels of miR-31. Other transcription factors, such as NF-κB and AP-1, can also influence miR-31 expression, particularly in the context of inflammation and tumor progression (4, 24, 25, 26).

After transcription, pri-miR-31 undergoes processing in the nucleus by the Drosha complex, which includes the RNA-binding protein DGCR8. This complex recognizes the pri-miRNA's stem-loop structure and cleaves it to produce pre-miR-31, a shorter hairpin-shaped RNA approximately 70 nucleotides in length. This initial processing step is crucial, as it determines the efficiency and subsequent expression levels of the mature miRNA. The activity of the Drosha complex can be modulated by various cellular conditions, including oncogenic signals and the presence of specific co-factors that either enhance or inhibit the processing of pri-miR-31 (24, 25, 27).

Once pre-miR-31 is generated, it must be transported from the nucleus to the cytoplasm, a process mediated by the Exportin-5 protein in a Ran-GTP dependent manner. This step is critical, as it determines whether pre-miR-31 can undergo further processing in the cytoplasm. The efficiency of this transport can be affected by factors such as nucleocytoplasmic transport dynamics and the cellular context, including the tumor microenvironment. Any dysregulation in this step may lead to aberrant levels of miR-31, influencing CRC progression (27, 28).

In the cytoplasm, pre-miR-31 undergoes further processing by the enzyme Dicer, which cleaves the hairpin structure to produce a double-stranded RNA molecule comprising the guide strand (miR-31-5p) and the passenger strand (miR-31-3p). The selection of the guide strand is determined by the thermodynamic stability of the duplex, with the more stable strand being incorporated into the RNA-induced silencing complex (RISC), while the passenger strand is typically degraded. This processing is essential, as the incorporation of miR-31 into RISC is necessary for its subsequent regulatory functions

Once incorporated into RISC, miR-31 exerts its regulatory effects by binding to complementary sequences within target mRNAs, leading to their translational repression or degradation. miR-31 targets a wide range of mRNAs involved in various signaling pathways and cellular processes, including PTEN, AXIN2, and RASA1. By repressing tumor suppressor genes like PTEN, miR-31 enhances signaling through pathways such as the PI3K/AKT and Wnt/β-catenin pathways, contributing to cell proliferation, survival, and metastasis. This oncogenic activity underscores the role of miR-31 in promoting CRC progression the expression and biogenesis of miR-31 are heavily influenced by the tumor microenvironment and various oncogenic signals prevalent in CRC. For instance, mutations in the KRAS gene, which are common in CRC, can lead to the upregulation of miR-31 by activating downstream signaling pathways that enhance its transcription additionally, pro-inflammatory cytokines and growth factors abundant in the tumor microenvironment can modulate miR-31 expression. The interplay between these signals and miR-31 biogenesis is critical, as it determines the miR-31 levels that contribute to CRC progression (5, 22, 23, 25, 27, 31, 32).

Elevated levels of miR-31 in CRC correlate with aggressive tumor characteristics, including increased cell proliferation, enhanced migratory capabilities, and resistance to apoptosis. These features are crucial for the metastatic potential of CRC, as miR-31 facilitates processes such as epithelial-mesenchymal transition (EMT). miR-31 directly downregulates E-cadherin while upregulating N-cadherin and vimentin, promoting the invasive properties of CRC cells. Furthermore, miR-31's role in inhibiting apoptotic pathways allows CRC cells to survive aggressive therapeutic interventions, thereby contributing to chemoresistance (32, 33, 34).

Understanding the biogenesis and functional roles of miR-31 provides valuable insights for potential therapeutic interventions in CRC. Targeting the regulatory pathways upstream of miR-31 expression, such as inhibiting Wnt signaling or utilizing small-molecule inhibitors to downregulate KRAS activity, may reduce miR-31 levels, restoring the activity of its target tumor suppressors. Moreover, developing specific miR-31 inhibitors could enhance the effectiveness of chemotherapeutic agents by sensitizing CRC cells to apoptosis. In conclusion, the intricate biogenesis of miR-31, its regulation by oncogenic signals, and its significant

implications for CRC pathophysiology underscore the potential for miR-31 as a target for innovative therapeutic strategies aimed at improving outcomes for patients with colorectal cancer (figure 1)(32, 33, 35).

The Role of miR-31 in the Pathogenesis of Colorectal Cancer

miR-31 in Colorectal Cancer Pathogenesis

miR-31 has garnered considerable attention as a pivotal regulatory molecule in the pathogenesis of colorectal

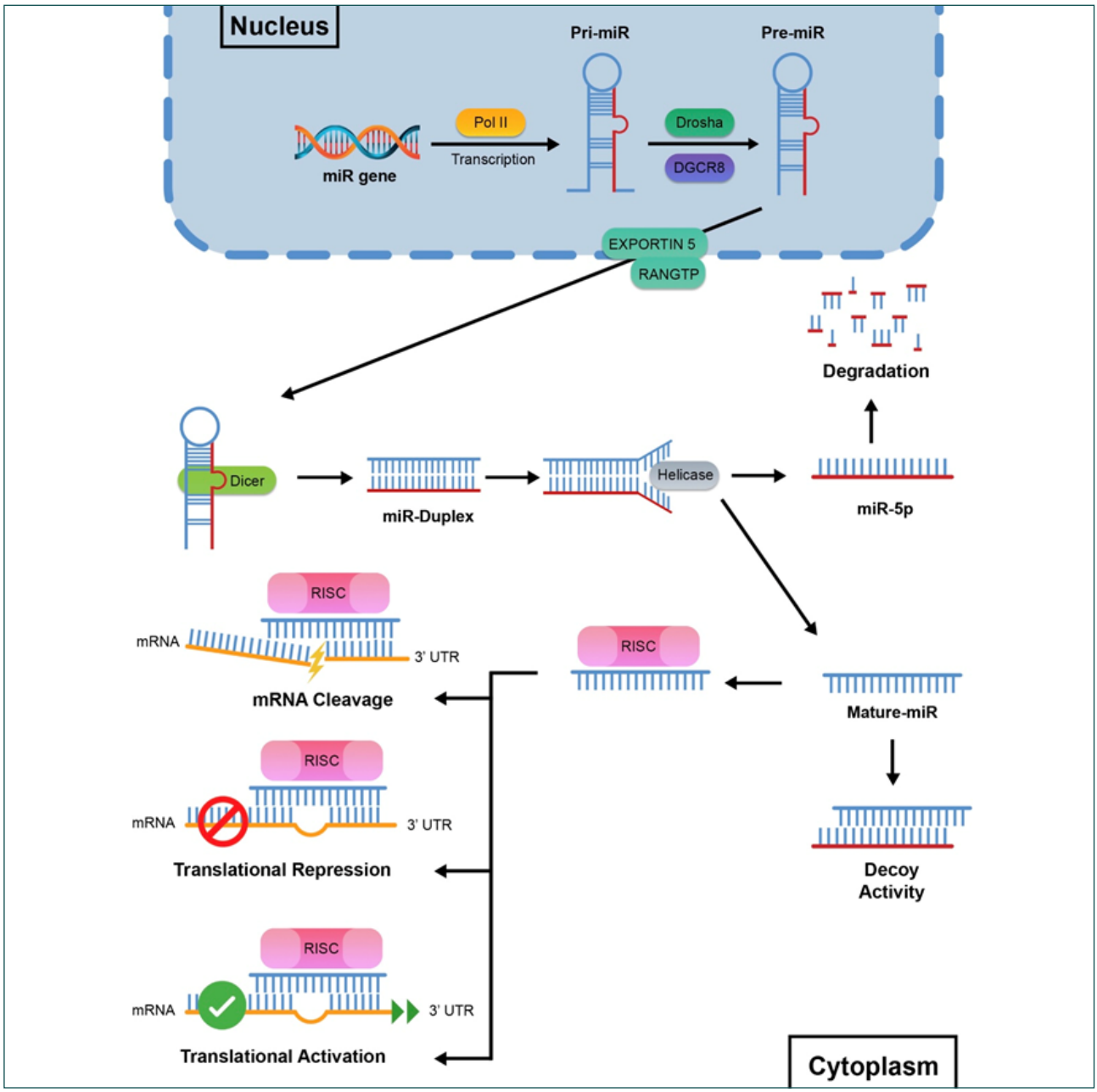

Figure 1. miRNAs play a crucial role in regulating gene expression and mRNA degradation. This process involves key molecules such as RNA polymerase II and III (RNA pol II/III) for transcription, METTL3 for RNA methylation, DGCR8 for miRNA processing, Ran-GTP for nucleocytoplasmic transport, and TRBP for gene silencing. These components work together within the RNA-induced silencing complex (RISC), which regulates mRNA degradation and gene expression, also influenced by Toll-like receptor (TLR) signaling (figures are designed using graphic design software such as Adobe Photoshop and Adobe Illustrator).

cancer (CRC). Its dysregulation is implicated in various aspects of tumor biology, including growth, invasion, metastasis, and resistance to therapy. Characterized predominantly as an oncogenic microRNA, miR-31 orchestrates a complex interplay of signaling pathways and cellular processes critical for tumorigenesis. This comprehensive overview elucidates the molecular mechanisms underlying miR-31's role in CRC and discusses its potential as a biomarker and therapeutic target (35, 36).

- Biogenesis of miR-31

The biogenesis of miR-31 begins at its genomic locus, which is located within the matrix metalloproteinase 2 (MMP2) gene. The transcription of pri-miR-31 is predominantly mediated by RNA polymerase II, generating a long primary transcript characterized by a stem-loop structure essential for subsequent processing. The expression of pri-miR-31 is influenced by various oncogenic signals, notably the Wnt/β-catenin pathway. Upon activation, β-catenin translocates to the nucleus and interacts with TCF/LEF transcription factors, enhancing the transcription of miR-31 (37, 38). Other factors, including NF-κB and AP-1, also contribute to the regulation of miR-31 expression, particularly in the context of inflammation and tumor progression (38).

Following transcription, pri-miR-31 undergoes initial processing in the nucleus by the Drosha complex, consisting of the RNA-binding protein DGCR8. This complex recognizes the stem-loop structure of pri-miR-31 and cleaves it to produce pre-miR-31, a shorter hairpin-shaped RNA of approximately 70 nucleotides. This processing step is crucial, as it determines the efficiency and subsequent levels of mature miR-31. Various cellular factors can modulate Drosha activity, affecting the processing of pri-miR-31 in response to oncogenic signals (39).

Once pre-miR-31 is generated, it is transported from the nucleus to the cytoplasm by Exportin-5 in a Ran-GTP-dependent manner. This export is vital for the maturation of miR-31, as pre-miR-31 must undergo further processing in the cytoplasm. In this compartment, Dicer enzyme processes pre-miR-31, cleaving the hairpin structure to yield a double-stranded RNA molecule comprising the guide strand (miR-31-5p) and the passenger strand (miR-31-3p). The thermodynamic stability of the duplex determines which strand is incorporated into the RNA-induced silencing complex (RISC), with the guide strand being preferentially selected for this incorporation. The passenger strand is typically degraded, a process essential for the regulatory functions of miR-31 (fighter 2) (40).

The oncogenic properties of miR-31 in CRC are multifactorial, influencing several critical signaling pathways that drive cancer progression.

1. Regulation of the Wnt/β-Catenin Pathway: One of the primary pathways modulated by miR-31 is the Wnt/β-catenin signaling pathway, which plays a central role in CRC development. miR-31 targets negative regulators such as AXIN2 and GSK3β, leading to their downregulation. This inhibition results in the stabilization of β-catenin, allowing it to translocate into the nucleus where it activates target genes involved in cell proliferation, including CCND1 (cyclin D1) and MYC (41, 42). The activation of this pathway enhances cancer cell survival and promotes stem-like properties, facilitating tumor initiation and progression.
2. Activation of Ras/Raf/MEK/ERK Pathway: miR-31 is also critically involved in the Ras/Raf/MEK/ERK signaling cascade, essential for cell growth and survival. It directly targets RASA1 and SPRY2, both negative regulators of Ras signaling. By downregulating these proteins, miR-31 sustains Ras activation, leading to persistent signaling through the Raf/MEK/ERK pathway. This results in the activation of transcription factors such as ELK1 and AP-1, which drive oncogenic gene expression and promote CRC cell proliferation, survival, and invasion (43, 44).
3. PI3K/AKT/mTOR Signaling Activation: The PI3K/AKT/mTOR signaling axis is frequently dysregulated in CRC and is crucial for cell survival and chemoresistance. miR-31 downregulates PTEN, a key tumor suppressor that inhibits the PI3K/AKT pathway. This downregulation leads to hyperactivation of AKT, which subsequently activates mTOR, driving metabolic reprogramming and protein synthesis favorable for cancer cells (45, 46). Additionally, the activation of this pathway contributes to chemoresistance by promoting cell survival in the face of therapeutic agents such as 5-fluorouracil (5-FU) and oxaliplatin (45,46,47) (Figure 3)

- Role in Epithelial-Mesenchymal Transition (EMT) and Metastasis

miR-31 serves as a critical regulator of epithelial-mesenchymal transition (EMT), a key process that enhances the invasive capabilities of tumor cells. During

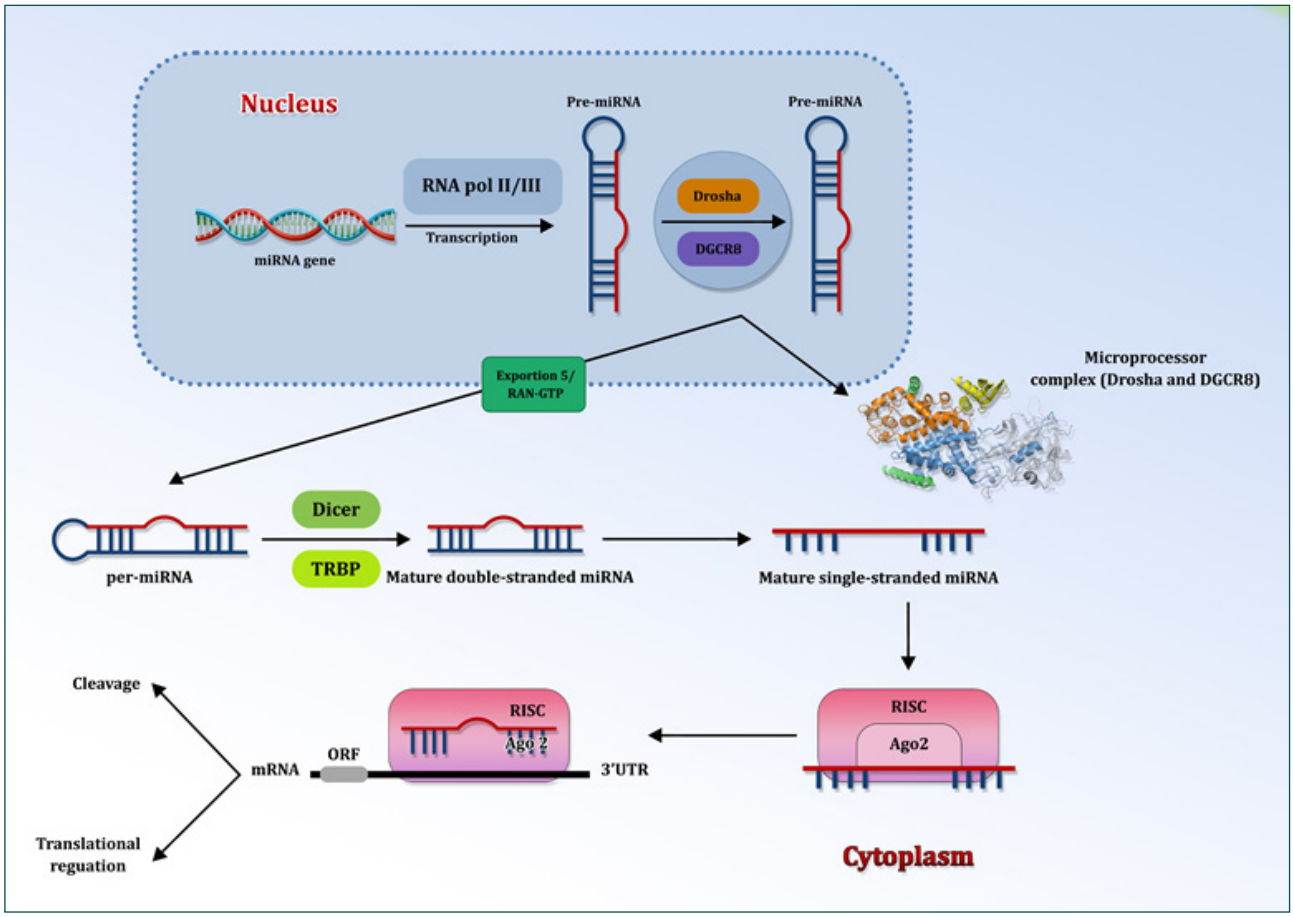

Figure 2. The primary microRNA transcript (pri-miRNA) is transcribed by RNA polymerase II or III (RNA pol II/III). This transcript is then processed in the nucleus by the Drosha-DGCR8 complex into a precursor microRNA (pre-miRNA). The pre-miRNA is exported from the nucleus to the cytoplasm with the help of the Ran-GTP protein. In the cytoplasm, the Dicer enzyme, along with the TAR RNA-binding protein (TRBP), processes the pre-miRNA into smaller RNA duplexes. Finally, one strand of the duplex is incorporated into the RNA-induced silencing complex (RISC) with the Argonaute (Ago) protein, enabling it to regulate target mRNA expression (figures are designed using graphic design software such as Adobe Photoshop and Adobe Illustrator).

EMT, epithelial cells lose their adhesion properties and acquire mesenchymal characteristics, facilitating migration and invasion. miR-31 downregulates E-cadherin, an essential epithelial marker while upregulating mesenchymal markers such as N-cadherin and vimentin (47, 48). Moreover, miR-31 influences the expression of transcription factors associated with EMT, including ZEB1, SNAIL, and TWIST. Through these mechanisms, miR-31 significantly enhances the invasive potential and metastatic dissemination of CRC cells, contributing to poor patient outcomes.

Inhibition of Apoptosis and Chemoresistance

In CRC, miR-31 plays a critical role in inhibiting apoptosis, allowing cancer cells to evade programmed cell death. By targeting pro-apoptotic factors such as BAX and Caspase-3, miR-31 impedes the activation of apoptotic pathways, promoting cell survival (49, 50, 51, 52). This anti-apoptotic function is particularly significant in the context of chemotherapy, where miR-31 has been associated with resistance to commonly used agents. It enhances the expression of anti-apoptotic proteins such as Bcl-2 and MCL1, which further protect CRC cells from drug-induced apoptosis. The ability of miR-31 to confer chemoresistance is a crucial aspect of its oncogenic profile and presents significant challenges in CRC treatment (53,54).

Clinical Relevance and Biomarker Potential

The clinical implications of miR-31 expression levels in CRC are profound. Elevated levels of miR-31 have been correlated with advanced tumor stages, increased

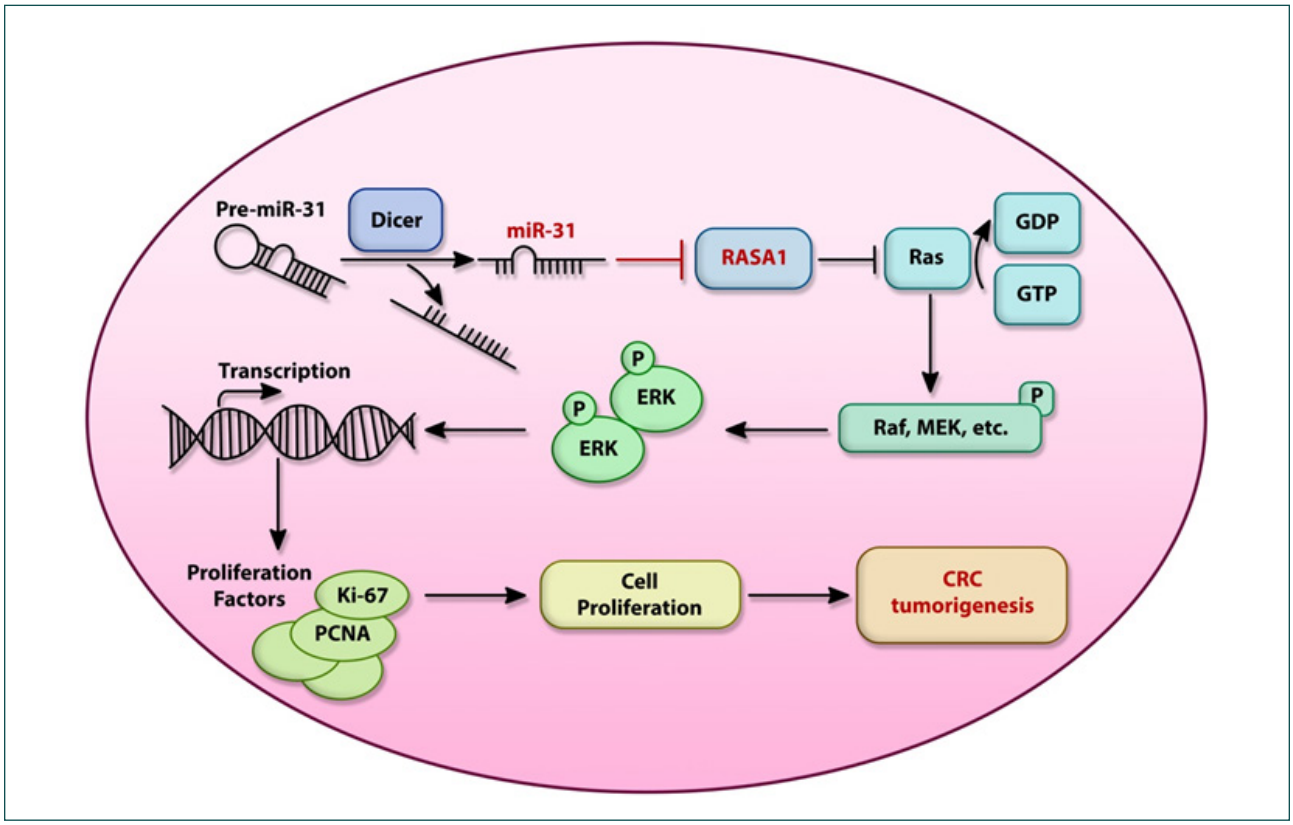

Figure 3. The role of miR-31 in regulating signaling pathways associated with cell proliferation and tumorigenesis in CRC. Following processing by the enzyme Dicer, miR-31 suppresses the expression of RASA1, thereby activating the Ras pathway and converting Ras into its active GTP-bound form. This activation triggers downstream signaling proteins such as Raf, MEK, and ERK through phosphorylation, promoting transcriptional changes that enhance cell proliferation. Consequently, proliferation markers such as Ki-67 and PCNA are upregulated, leading to uncontrolled cell growth and tumorigenesis. Overall, miR-31 facilitates CRC progression by modulating the Ras/ERK signaling pathway (figures are designed using graphic design software such as Adobe Photoshop and Adobe Illustrator).

metastatic potential, and poorer patient prognosis (51, 52). These associations suggest that miR-31 could serve as a valuable biomarker for assessing CRC risk and prognosis, providing clinicians with critical information for treatment decisions. Monitoring miR-31 levels in patients may help identify those at higher risk for aggressive disease who could benefit from more intensive therapeutic strategies.

Additionally, targeting miR-31 presents a promising therapeutic avenue. Strategies aimed at inhibiting miR-31 expression, such as the use of specific miR-31 antagonists or inhibitors, could reduce its levels in CRC cells and restore the function of its target tumor suppressors (53, 54). Moreover, targeting upstream signaling pathways that regulate miR-31 expression, such as Wnt signaling or KRAS activity, may provide a complementary approach to reducing miR-31 levels and enhancing treatment efficacy.

Future Directions in Research and Therapeutics

The ongoing research into miR-31's role in CRC pathogenesis opens new avenues for therapeutic interventions. Understanding the interplay between miR-31 and the tumor microenvironment, including its influence on immune responses and inflammatory pathways, is essential for developing comprehensive treatment strategies (55, 56). Investigating combination therapies that target miR-31 alongside conventional chemotherapeutics could enhance treatment effectiveness and overcome resistance mechanisms, providing a more integrated approach to CRC management.

Furthermore, exploring the potential of miR-31 as a target for gene therapy or the development of novel delivery systems for miR-31 inhibitors could represent a significant advancement in CRC therapy. Such approaches could potentially improve patient outcomes by sensitizing CRC cells to chemotherapy and reducing

tumor aggressiveness (57, 58).

Assessment of miR-31 in Colorectal Cancer

The exploration of miR-31 in CRC has revealed its significant potential as a diagnostic and prognostic biomarker. Elevated expression levels of miR-31 have been consistently observed in both plasma and tissue samples from CRC patients, correlating with disease progression and poorer clinical outcomes. These findings underscore miR-31's role as a valuable biomarker for early diagnosis and prognosis of CRC (57, 58).

Recent studies utilizing quantitative real-time PCR (qRT-PCR) and TaqMan assays have demonstrated markedly increased miR-31 levels in the plasma of CRC patients compared to healthy controls. This elevation in miR-31 expression is significantly associated with advanced tumor stages and metastasis, making it a critical factor for assessing the aggressiveness of the disease (59, 60). Importantly, miR-31 expression is also heightened in precancerous lesions such as colorectal adenomas, indicating its potential utility in the early detection and monitoring of CRC (61,62).

The assessment of circulating miR-31 offers several advantages as a non-invasive diagnostic tool. Its presence in body fluids like plasma allows for the development of less invasive screening methods compared to traditional tissue biopsies, which can be more painful and expensive. Additionally, the stability of circulating miR-31 in the bloodstream, coupled with its dynamic expression changes throughout tumorigenesis, enhances its specificity and sensitivity as a biomarker (62,63).

In the context of CRC, the regulation of miR-31 is intricately linked to various signaling pathways, particularly those involving oncogenes and tumor suppressors. For instance, miR-31 is known to target the tumor suppressor PTEN, leading to its downregulation and consequently promoting the activation of the PI3K/AKT pathway, which is critical for cell proliferation, survival, and metastasis (63,64). The alteration of miR-31 levels in CRC tissues further reflects its involvement in the tumor microenvironment and the pathogenesis of the disease (64,65,66).

Moreover, studies have indicated that miR-31 levels can fluctuate during the stages of CRC development, making it a potential indicator of tumor dynamics and response to therapy. Assessing miR-31 in conjunction with other biomarkers may enhance the overall diagnostic accuracy and prognostic capability for CRC, allowing for a more personalized approach to treatment (figure 4) (57, 59,65,67).

In this study, which was conducted by Moloudizargari and colleagues in America and Iran in 2022, to investigate the relationship between miR-31 expression and clinical outcomes in colorectal cancer (CRC). In this study, a meta-analysis of 16 studies showed that high miR-31 expression was significantly associated with poor overall survival (OS) and progression-free survival (PFS). Furthermore, patients with high miR-31 levels were more likely to have BRAF mutations, and the observed results were influenced by treatment regimens and mutation status. High miR-31 expression has also shown predictive value for response to anti-EGFR therapies (68).

Conclusion

Altered expression of miRNAs, particularly miR-31 has been implicated in a variety of cancers, including CRC, breast cancer, and pancreatic cancer. These microRNAs are crucial regulators of cellular processes that drive cancer progression, including cell proliferation, migration, differentiation, and apoptosis. In recent studies, increased levels of miR-31 have been associated with advanced stages of CRC, suggesting its potential as a diagnostic biomarker.

Evidence shows that elevated miR-31 expression can be detected in the serum of patients, even at the early stages of CRC, indicating its promise as a non-invasive biomarker for early diagnosis. The ability to monitor miR-31 levels in blood samples makes it a valuable addition to existing diagnostic methods, providing a more cost-effective and less invasive alternative for CRC screening.

Given the significant roles miRNAs play in cancer development, miR-31 stands out as a critical factor in CRC initiation and progression. It can act either as an oncogene, promoting tumor growth and metastasis, or potentially exhibit tumor-suppressive effects under certain conditions. This dual functionality highlights the importance of miR-31 as both a biomarker for early detection and a target for therapeutic interventions in CRC. As research continues to unravel the complexities of miRNA biology, miR-31 may serve as a focal point for future studies aimed at developing innovative diagnostic and therapeutic strategies in colorectal cancer management.

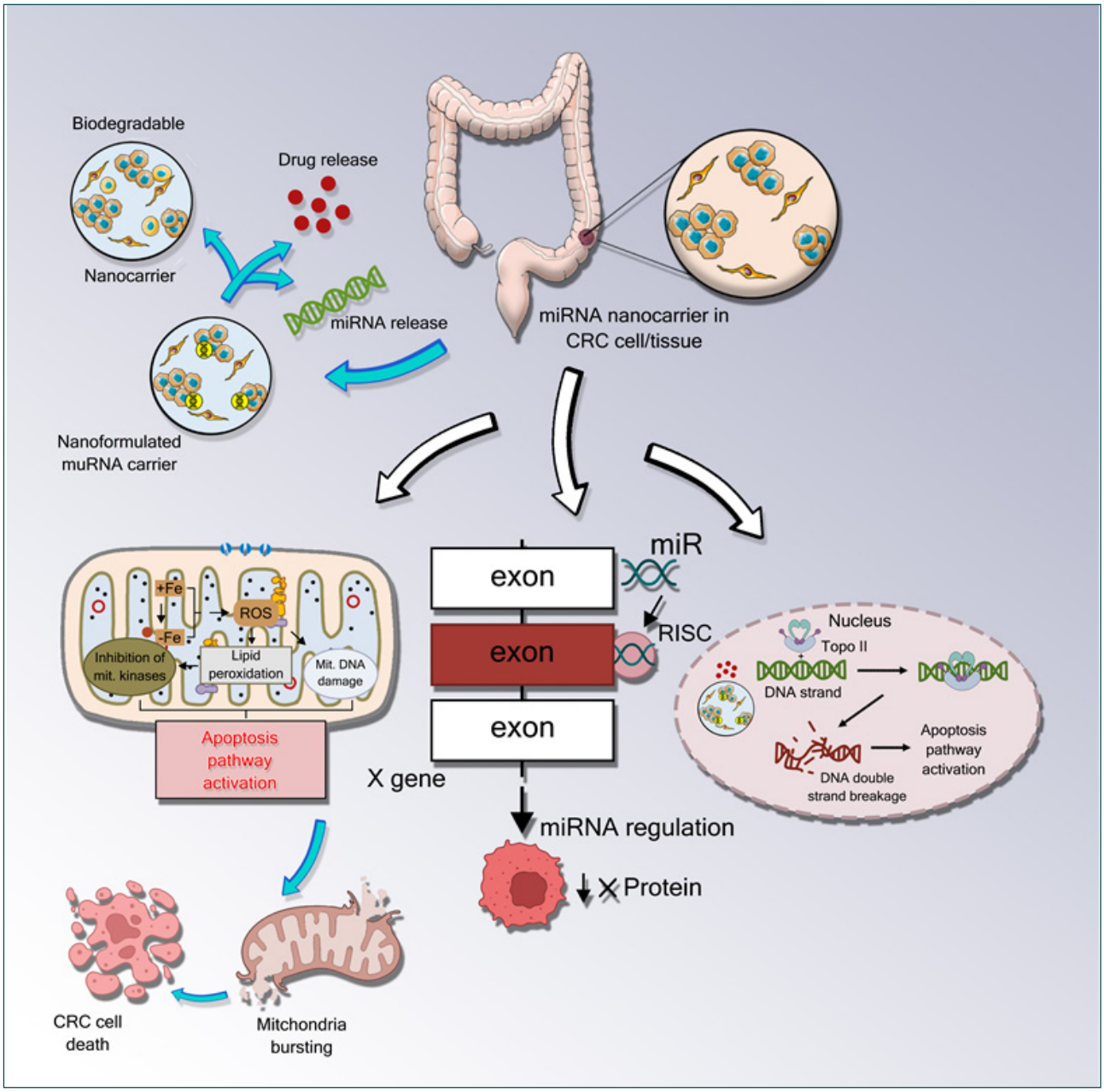

Figure 4. This diagram illustrates the use of miRNA-based nanocarriers for colorectal cancer (CRC) therapy. The process begins with biodegradable nanocarriers delivering miRNA formulations directly to CRC cells. Released miRNAs enter the cells and integrate into the RNA-induced silencing complex (RISC), targeting specific genes to reduce harmful protein expression. Additionally, miRNA actions contribute to mitochondrial damage through mechanisms such as iron dysregulation, reactive oxygen species (ROS) generation, lipid peroxidation, and mitochondrial DNA damage. These effects ultimately activate apoptosis pathways, leading to cancer cell death (figures are designed using graphic design software such as Adobe Photoshop and Adobe Illustrator).

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