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Roles of miR-21 in the Onset and Advancement of Colorectal Cancer (CRC)

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MiR-21 is a critical small regulatory RNA involved in various cellular processes such as cell cycle, apoptosis, migration, and differentiation of stem cells. It is significantly upregulated in CRC cell lines and tissue samples, acting as a biomarker and playing an important role in the pathogenesis of CRC. MiR-21 targets and downregulates tumor suppressor genes such as PDCD4, which are part of the PI3K-mTOR pathway. The inverse relationship between miR-21 and PDCD4 expression highlights the miR-21 role in CRC progression. Research shows that miR-21 is upregulated in human CRC cell lines and tissue samples, correlating with advanced clinical stages, lymph node metastasis, and poor prognosis. This regulation highlights the potential of miR-21 as a biomarker for the early detection of CRC and as a therapeutic target for developing targeted therapies. MiR-21 regulates several CRC-related target genes, highlighting its role in cancer initiation, transformation, invasion, and metastasis. These findings provide valuable insights into miR-21's role in cancer pathogenesis and its potential clinical applications.

INTRODUCTION

Small non-coding RNA known as microRNA (miRNA) controls post-transcriptional gene regulation. About 2000 human miRNAs exist, which are highly conservedin all eukaryotes [1,2]. Because miRNAs are stable and found in body fluids, they are important biomarkers of disease. One such miRNA, miR-21 is involved in several metabolic and biological processes, such as the cell cycle, apoptosis, migration, and stem cell development. MiR-21 plays a critical role in cancer development, transformation, invasion, and metastasis. Tumor suppressor gene Programmed Cell Death 4 (PDCD4) exhibits an inverse connection with miR-21 in tissues and tumor cell lines, including colorectal cancer (CRC) [3,4]. Research has shown that miR-21 levels are elevated in human colorectal cancer cell lines and tissue. Samples serve as a biomarker and play a vital role in all stages of CRC pathogenesis. These findings suggest that miR-21 regulates numerous CRC related target genes, highlighting its potential role in CRC through modulation of these genes. It is crucial to understand the mechanisms of action of miR-21 and to identify its downstream targets involved in inflammatory pathways and tumorigenesis in CRC. These molecules are potential therapeutic targets for the development ofCRC-specific treatments [2, 5, 6].

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1. 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].

2. miRNA structure and biogenesis

MiRNA can control at least 30% of the genes that encode for 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 has been shown to be clinically relevant to cancer diagnosis, progression, and outcome [14].

3. miR-21 functions

miRNA sequences are distributed throughout the genome, including exonic and intronic regions and intergenic sequences. Transcription of miRNAs is initiated by RNA polymerase II [2]. In some transcriptions, miRNAs are transcribed, making it possible to synthesize primary strands called pri-miRNAs which adopt a hairpin structure and are subsequently cleaved by the human microprocessor complex drosha a class 2 ribonuclease III enzyme (DRosha) and its related cofactor, the human DiGeorge syndrome critical region eight (DGCR8) protein, located in the nucleus to produce pre-miRNA [2]. After pre-miRNA production, exportin5, a protein bound to double-stranded RNA dsRNA and dependent on Ran-GTP, delivers pre-miRNAs to the cytoplasm,

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which occurs in a GTP-dependent process. Another activity of exportin5 is to protect the pre-miRNA from nuclear degradation [2]. In the cytoplasm, pre-miRNA undergoes further processing (cleavage of the loop region) by Dicer or the endoribonuclease Dicer with the transactivating response TAR RNA-binding protein (TRBP), resulting in miRNA duplexes [5]. Dicer is a type of protein that is necessary for the maturation of miRNAs and must be precisely regulated [2]. Its existence and function are essential and significant, so that the absence of Dicer is lethal. After converting the miRNA duplexes into single-stranded miRNAs, Argonaute (Ago) proteins form RNA-induced silencing complexes (RISC). The final RISC complex binds to the target mRNA via complementarity between the miRNA sequence and specific sites on the mRNA [3]. They originate within the introns of coding genes and are generated as pre-miRNAs during splicing, known as miRtrons (a type of miRNA located within mRNA intron near to exons), and play an important role in various diseases, especially cancer [2]. miRNAs regulate post-transcriptional gene expression through several mechanisms: they can repress translation by binding to target mRNAs, inhibit the initiation of translation, direct mRNA degradation, or control the storage or destruction of mRNAs in P-bodies. These processes play crucial roles in gene expression regulation and can significantly impact cellular functions [2] [Fig. 1].

4. Biogenesis of miR-21 in CRC cell lines

In CRC cell lines, miR-21 is induced by several vital mechanisms. RNA polymerase II/III initially converts miR-21 into a primary miRNA (pri-miRNA) with a hairpin structure. The Drosha-DGCR8 complex in the nucleus then processes this pri-miRNA to generate precursor miRNA (pre-miRNA). Exportin-5 transports the pre-miRNA to the cytoplasm, where Dicer processes it into a mature miRNA duplex. Normally, one strand of this duplex is destroyed when the leader strand (miR-21-5p) is incorporated into the RNA silencing complex (RISC). miR-21 targets tumor suppressor genes and promotes cell proliferation, migration, and invasion. Its expression in CRC cell lines contributes significantly to cancer progression. Increased levels of miR-21 in CRC are due to both transcriptional activation and post-transcriptional regulatory mechanisms [2, 19, 20]. The intronic region of the TMEM49 gene contains the pri-miRNA gene, which encodes for this miRNA. Pri-miR-21 is eventually converted to miR-21 after transcription [20]. Cell cycle, apoptosis, migration, differentiation, and self-renewal of stem cells are all important processes regulated by miR-21. These targets are also involved in cancer development, invasion, and metastasis [2]. Most research on miR-21 has focused on its therapeutic utility and function in carcinogenesis [21]. As mentioned above, the expression of miR-21 is abnormal in CRC, which is related to these patients' progress and poor prognosis [2]. Therefore, it is important to understand the mechanisms of action of miR-21 and identify its downstream targets in CRC [20]. One of the direct target genes of Programmed Cell Death (PDCD4) is miR-21. PDCD4 acts as a tumor suppressor gene downstream of the PI3K-mTOR pathway, and its expression level has shown an inverse relationship with miR-21 in some tissues and tumor cell lines, such as CRC [20]. This inverse relationship was observed in each stage of tumor progression (Dukes stage C, B, A, and D), suggesting that miR-21 may negatively regulate the PDCD4 mRNA levels in each CRC tumor stage [20]. In addition, Asangani and his colleagues investigated the inhibition of PDCD4 by miR-21. They found that overexpression of miR-21 resulted in increased invasion and metastasis of tumor cells transplanted into the mouse model [22]. PDCD4 is Also negatively regulated by miR-21, which induces invasion and metastasis in Colo206f cells [22]. When these cells were transfected with miR-21, the PDCD4 3'-UTR-containing luciferase reporter was significantly inhibited, and miR-21 expression increased in Colo206f. However, despite the severe reduction of PDCD4 protein, its mRNA expression did not change [22].

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In contrast, RKO transfection with anti-miR-21 increased the activity of this structure and these cells were able to increase PDCD4 protein expression, suggesting that PDCD4 is negatively

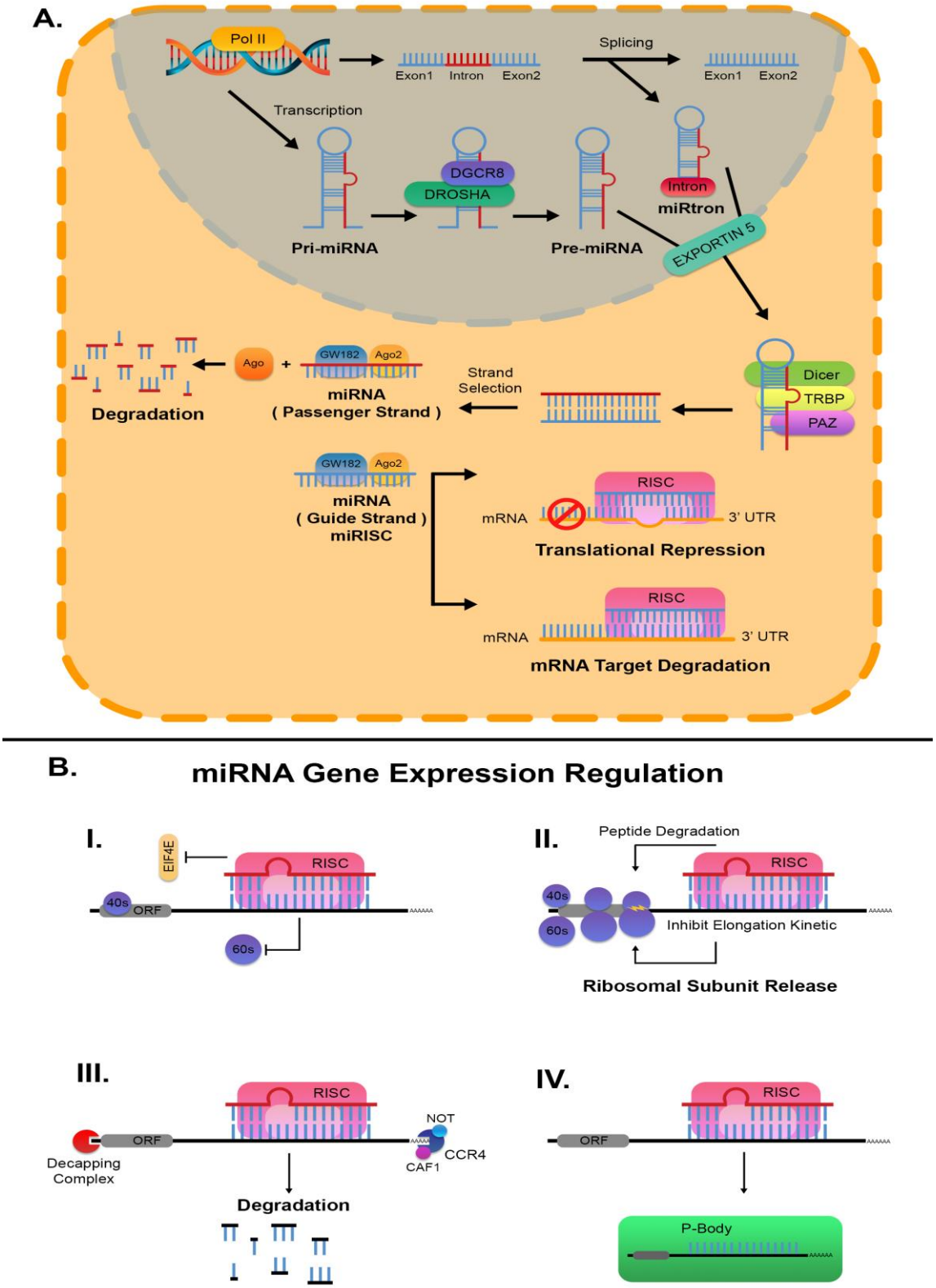

Figure 1. Pathway of biogenesis of miRNAs in the cells.

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controlled by miR-21 [22]. Similarly, increasing the expression of miR-21 in HCT-116 cells by stable transfection decreased the expression of PDCD4 [23]. A tumor suppressor gene named Spry2 (Sprouty2) is another target of the miR-21 gene [23]. Sprouty family members are involved in receptor tyrosine kinase signaling in response to growth factors and regulate the MAP kinase pathway [23]. A study reported that Spry2 inhibits the growth of the HCT-11 CRC cell line and leads to the promotion of apoptosis and induction of sensitivity to 5-FU and metformin; however, with the knockdown of miR-21 in these cells, the expression of Spry2 increases and leads to a decrease in the proliferation rate of HCT-116 cells, indicating that the function of Spty2 in CRC is regulated by miR-21 [22]. Phosphatase and tensin homolog (PTEN) acts by negatively regulating the PI3K-AKT signaling pathway and is mutated as a tumor suppressor gene in various cancers and regulates the proliferation, growth, and apoptosis of cells [23]. Studies have shown that the expression and production of phosphatase and tensin homolog (PTEN) is significantly reduced in tumor tissues compared to surrounding non-tumor tissues [22].

Dendritic cells, B/T cells, monocytes, macrophages, and other hematopoietic immune system cells express miR-21 [2]. Therefore, high levels of miR-21 are thought to immune cell activity [2]. By adversely affecting tumor suppressor genes associated with the death receptor-mediated innate apoptotic cascade, miR-21 facilitates pathological necrosis by inducing cell necrosis [24].

The formation of new blood vessels, or angiogenesis, is significantly supported by miR-21 [2]. This mechanism is important in healthy physiological states as well as in the development of diseases such as cancer. The AKT and ERK signaling pathways are required for cell migration, proliferation, and survival; MiR-21 facilitates these pathways. Vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1-alpha (HIF-1α) show increased expression in response to this pathway activation [2, 24-26]. In addition, miR-21 specifically targets and inhibits the tumor suppressor gene PTEN, leading to the activation of the AKT and ERK pathways and the promotion of angiogenesis [25, 26].

miR-21 and its exosomal form, which are involved in the cellular process that degrades and recycles cellular components, play an essential role in regulating autophagy. MiR-21 binds Phosphatase and Tensin Homolog (PTEN); Ras-related protein Rab-11A (Rab11a); Autophagy-Related 12 (Atg12); Several autophagy-related genes are targeted, such as Signal-Induced Proliferation-Associated 1-like 2 (SIPA1L22). and Autophagy-Related 5 (ATG5); indicating its essential role in this process. Exosomal miR-21: In particular, miR-21-5p has been shown to regulate autophagic flux by promoting vascular endothelial repair in conditions such as atherosclerosis-like signal-induced proliferation-associated 1 Like 2 (SIPA1L2). This regulation helps maintain cellular homeostasis and influences a variety of diseases, including cancer and cardiovascular disease [27, 28].

miR-21 plays a crucial role in apoptosis, or programmed cell death, by targeting various tumor suppressor genes that are often elevated in cancer. By targeting these genes, miR-21 promotes tumor growth and survival, allowing cancer cells to evade apoptosis. Among the key genes targeted by miR-21 in apoptosis are PTEN, which negatively regulates the PI3K/AKT pathway, essential for cell survival and proliferation; Bcl-2, an anti-apoptotic protein that helps cells resist programmed cell death; PDCD4, a tumor suppressor that promotes apoptosis and inhibits tumor progression; and TPM1, a gene involved in the cytoskeleton and apoptosis regulation. By downregulating these and other target genes, miR-21 disrupts normal apoptotic processes, allowing cancer cells to survive and proliferate [29, 30].

miR-21 enhances the activity of the transforming growth factor-beta (TGF-β)/SMAD-2/3 signaling pathway by targeting and downregulating SMAD family member 7 (SMAD7), an inhibitory SMAD protein. SMAD7 normally suppresses the TGF-β/SMAD signaling pathway by inhibiting the

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phosphorylation of SMAD family member 2 (SMAD2) and SMAD family member 3 (SMAD3). When miR-21 downregulates SMAD7, this inhibition is removed, resulting in increased phosphorylation and activation of SMAD2 and SMAD3. These phosphorylated SMAD proteins form a complex with SMAD4 and translocate to the nucleus, stimulating the transcription of TGF-β responsive genes. This enhanced signaling contributes to various pathological conditions, including fibrosis and cancer progression [31, 32]. miR-21 plays a crucial role in various cellular processes, including angiogenesis, autophagy, apoptosis, and the TGF-β/SMAD signaling pathway. Its regulatory role in these pathways highlights its importance in normal physiological functions and the progression of diseases such as cancer and cardiovascular disease. Understanding the mechanisms by which miR-21 functions provides valuable insights into its potential as a therapeutic target and offers promising avenues for future research and treatment strategies [33, 34] [Fig. 2].

5. The role of miR-21 in the pathogenesis of colorectal cancer

Among the various molecular factors involved in CRC, miR-21, a small regulatory RNA, has emerged as a crucial player. miR-21 is notably upregulated in CRC, influencing key processes such as inflammation, tumorigenesis, and metastasis. Understanding the role of miR-21 provides valuable insights into CRC pathogenesis and potential therapeutic strategies [2, 35].

Risk factors for CRC include obesity, diet and lack of fruits and vegetables, physical inactivity, and smoking [25]. These factors are mainly observed in developed countries involved in this disease [25]. Cancer results from a complex multi-step process involving multiple sequential changes in genes, especially genes encoding miRNA [3]. Some studies have also shown the effect miR-21

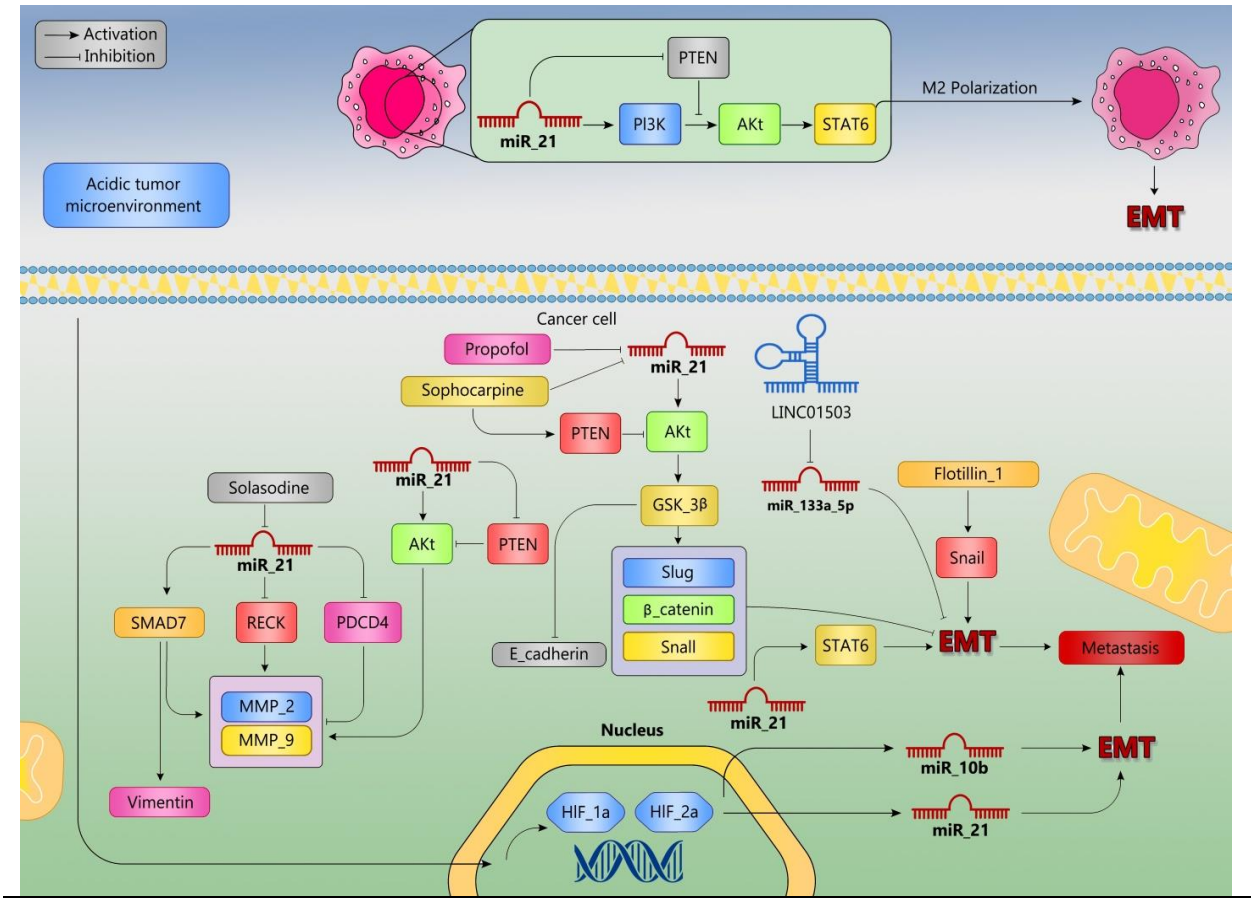

Figure 2. miR-21 signaling in cancers in human.

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on genes involved in inflammation and tumorigenesis, such as cyclooxygenase 2 /prostaglandin endoperoxide synthase 2 (COX2/PTGS2) [26, 36]. Increased expression of COX2/PTGS2 and its product PGE2, which are involved in the induction of inflammatory pathways and tumorigenesis, has been observed in CRC [26]. Researchers have observed that the high level of miR-21 expression and the high level of gene expression involved in inflammatory responses in CRC are related [26]. Also, miR-21 reduces the expression of gene products that catalyze the degradation of PGE2 and accelerate tumor growth in a xenograft model [2]. In this context, his colleagues observed a significant interaction between the expression level of miR-21 and PTGS1 and suggested that the unfavorable prognosis relationship in tumors with high expression of miR-21 is more severe in cancers with high PTGS2 than in cancers with low PTGS2 or lack of PTGS2 [36].

Numerous pieces of evidence indicate that most human cancers exhibit abnormal miRNA expression patterns [3]. The multi-step process leading to genetic alterations that cause cancer impacts numerous biochemical pathways, including recently identified non-coding genes and genes that encode for specific proteins [37]. miRNAs, which regulate mRNA translation to affect gene expression, are examples of non-coding RNAs [3]. Mutations in tumor suppressor and oncogene genes also regulate cancer. MiRNAs allow us to control how these genes are expressed [2]. Alterations in miRNA expression, such as amplification, deletion, and mutation, can affect the regulation of oncogenes and tumor suppressor genes [2]. Other mechanisms of cancer initiation and progression are less common in cancer, such as invasion, angiogenesis, metastasis, apoptosis, cell proliferation, growth, and DNA repair [20]. When tailored to account for the essential roles that the target proteins play in various pathways and signaling, miR-21 can be very helpful in the treatment of disease and the genetic and pharmacological modification of various disease situations [20].

Numerous investigations by scientists have validated the critical function of miR-21 in the pathogenesis of tumors and all other stages of carcinogenesis [2]. There is growing evidence that miR-21 expression is a significant biomarker in predicting cancer prognosis in both benign and malignant stages. Generally speaking, malignancies with higher levels of expression have more advanced cancers. According to these investigations, overexpression of miR-21 in colorectal cancer (CRC) was significantly associated with advanced clinical stage, lymph node metastasis, and a poor prognosis [2]. Research has demonstrated that elevated expression of miR-21 in human colorectal cancer cell lines cultured in laboratory settings and tissue samples functions as a biomarker and is essential for each stage of colorectal cancer (CRC) development, were expressed in the studies conducted in these cases [35]. In addition, miR-21 regulates protein expression by downregulating metastasis suppressors like P53 in CRC. Further studies have shown that miR-21 in serum, urine, and even saliva can serve as a potential diagnostic biomarker for CRC [36].

These findings indicate that miR-21 regulates many target genes related to CRC, and likely plays an important role in CRC by regulating these genes [35]. It has also been observed that the expression of PTEN has an inverse relationship with the expression of miR-21 in colorectal tumor tissues and HTC-116 cells, and miR-21 inhibition significantly suppresses the proliferation and migration ability of HTC cells. Inhibition of miR-21 can increase the expression of PTEN in HCT-116 cell lines, indicating that miR-21 can intensify the malignant biological condition by inactivating the target gene PTEN [38]. miR-21 alters the phosphorylation of focal adhesion kinase and the expression of matrix metalloprotease 2/9 (MMP2/9), both downstream mediators of PTEN and involved in migration and metastasis. Downregulation of PTEN by miR-21 probably leads to increased expression of the PI3K-AKT pathway or MMPs, ultimately increasing cell survival and motility. A luciferase assay is one of

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the common methods used to confirm the direct targets of miRNAs [38].

In the studies conducted by Xiong and his colleagues, they constructed luciferase reporter plasmids containing the wild-type or - 3'-UTR mutant of PTEN. They transfected them together with the miR-21 inhibitor into HCT-11 cells. They showed that the miR-21 inhibitor when added to transfected together with the wild-type reporter plasmid, reduced the relative activity of luciferase. However, this effect is associated with severe combined immunodeficiency (SCID) in mice [39]. In contrast, HCT-116 cells transfected with 2TGFβR stopped and lost the luciferase activity of TCF/LEF and reduced the expression of β-catenin, c-Myc, and cyclin-D, suggesting that miR-21 affects the message delivery of 2 TGFβR It plays an important role in regulating stemness [39]. Chemokine C-C motif Chemokine Ligand 20(CCL20) has been reported as another regulatory target of cancer cell lines in miR-21 in colorectal cancer cell lines. The expression of chemokine ligand CCL20 and its receptor is mainly increased in CRC, and it is involved in increasing the proliferation and migration of cancer cells. It has been reported that miR-21 regulates the expression of a luciferase construct containing the 3'-UTR of CCL20 mRNA [40]. Overexpression of miR-21 by miR-21 precursor transfection led to a significant decrease in the expression levels of the CCL20 gene, mRNA, and protein in two CRC cell lines (SW480)(SW620) and a significant decrease in the level of CCL20 protein only in the Caco-2 cell line [31]. RhoB is a family of small GTPases that can limit cell proliferation, survival, invasion, and metastasis in cancer [40]. It has been observed that overexpression of miR-21 or a RhoB small interfering RNA (siRNA) (si-RhoB) in SW1116 cells significantly enhances the proliferative ability of these cells while leading to a marked reduction in the rate of apoptosis [41].

Interestingly, SW1116 cells transfected with miR-21 or si-RhoB showed a significant increase in invasive activity, while similar inhibition of miR-21 or RhoB overexpression in Colo320 cells suppressed the prominent proliferative and aggressive activities of these cells [41]. On the other hand, enhanced cell apoptosis indicates that the messenger axis of miR-21-RhoB is bound in cell division cycle 25A(Cdc25A) 3'-UTR and under stress conditions, without affecting apoptosis, by suppressing its expression, it leads to regulation of cell cycle progress [41]. Serum deficiency and DNA damage induce miR-21 expression in colon cancer cells, while Cdc25A overexpression decreases miR-21 expression in colon cancers [40,41]. Similarly, hypoxia has been observed to decrease Cdc25A protein and mRNA levels in colon cancer cells, leading to S-phase arrest with a reduced mitotic population [41]. This reduction is dependent on p21 and miR-21, which are increased during hypoxia in colon cancer cells. In addition, Wang and colleagues showed that miR-21 suppresses the proliferation of RKO and DLD1 cells following serum deprivation and delays the G1/S transition through Cdc25A, as well as regulates DNA damage-induced G2/M checkpoint through Cdc25A regulates [42].

6. Assessment of miR-21 in colorectal cancer

The detection of miR-21 in CRC has emerged as a promising diagnostic tool. Elevated levels of miR-21 in plasma and tissue samples are strongly associated with CRC progression, making it a valuable biomarker for early diagnosis and prognosis. Utilizing miR-21 expression patterns can improve the specificity and sensitivity of CRC screening [2, 41-43].

According to a recent study, TaqMan analysis revealed a substantial increase in plasma miR-21 expression in CRC patients. Tumor prognosis is associated with miR-21 [43, 2]. Furthermore, miR-21 is frequently elevated even in premalignant lesions that are the focus of CRC screening, including colon adenomas [25]. In this work, we postulated that miR-21 is a promising candidate for further investigation as a biomarker [43].

This has led to studies demonstrating the diagnostic and prognostic value of circulating miRNAs, most of which have been conducted in tissue samples [44]. This is significant because

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altered expression levels of circulating miRNAs may reveal tumor-produced miRNAs and boost the diagnostic specificity of the biomarker [44].

PTEN is overexpressed in several human diseases. Malignancies and controls TPM1 and PDCD, which are associated with cancer. Furthermore, miR-21 expression is up- or downregulated in CRC tissues during tumorigenesis [43]. According to a recent study, TaqMan analysis revealed a significant increase in plasma miR-21 expression in CRC patients. Tumor prognosis is associated with miR-21 [2, 43].

Mir-21 is a useful non-invasive biomarker. Due to the specific characteristics of the tissue, there is stability and change in their expression during tumor development. To complement the current screening technique, miR-21 analysis may be a less invasive and cost-effective option [2, 43, 44].

CONCLUSION

We know that altered expression of miRNAs, especially miRNA-21, has been found in various cancers, including CRC, pancreatic, and breast. In contrast, microRNAs play an important role in cellular mechanisms of cancer development, such as cell proliferation, migration, differentiation, and apoptosis. The presence of miRNA has been proposed as a diagnostic tool for CRC. During studies, CRC with acute manifestations and advanced stages was associated with increased expression of miR-21 in serum and biopsy. miR-21 expression patterns in serum can be detected even in the early stages of malignant rectal cancer, making it a valuable non-invasive biomarker. MiRNAs are attracting attention as potential diagnostic, prognostic, and predictive biomarkers. Therefore, miR-21 analysis may be an additional, more cost-effective, and less invasive screening method to complement current methods. It is concluded that microRNAs are the most important factors involved in the initiation and progression of CRC. Therefore, these molecules are biomarkers in the early diagnosis of CRC and therapeutic elements in the production of CRC and target agents in future research. miRNAs, especially miRNA-21, can function as tumor suppressor genes or oncogenes.

We suggest further research to investigate how miRNAs can be used as therapeutic agents to suppress diseases or cancers. For example, we propose that siRNA molecules, similar to miRNAs, modulate the expression of cancer genes. Therefore, we recommend the use of micro and nanoformulation agents such as liposomes, peptide nanocarriers, micelles, MNPs, CNTs, QDs, dendrimers MSNs, and magnetic agents, as well as the use of elements in nanomaterials that have anti-cancer properties. A new method of delivering these molecules to cancer cells to target mRNA must be performed. And suppression of tumors in the early stages of development. For cancer initiation or progression, miRNA therapies may show promising results for CRC treatment in future studies.

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None declared.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

This study does not need an ethical approval number.

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