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Prominent roles of microRNA-142 in cancer

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Abstract

MicroRNAs (miRNAs) are single-stranded non-coding RNAs that regulate gene expression post-transcriptionally via mRNA degradation, or translational repression. They have important roles in normal development and homeostasis maintenance. Many studies have revealed that aberrant expression of miRNAs is associated with development of pathological conditions, including cancers. MiRNAs can either promote or suppress tumorigenesis based on the regulation of gene expression by

targeting multiple molecules. In recent years, several miRNAs have been reported to be dysregulated in various cancers. Most recent findings have shown that miR-142 gene, located at chromosome 17q22, is involved in cellular migration, proliferation, and apoptosis in different human cancers. The present review discusses some molecular mechanisms and the expression status of miRNA-142 in the pathogenesis of various cancers.

Keywords: Metastasis, Invasion, Cancer, miRNA-142, malignancies

1 Introduction

Currently, detecting the majority of cancers is challenging, especially at advanced stages, which makes it difficult to alleviate problems of patients [1]. Accordingly, detection of cancers at early stages significantly reduces the mortality rate. Development of new molecular biomarkers for cancer screening improved the introduction of potential molecular candidates for risk management, detection, and treatment follow-up [1]. Circulating microRNAs (miRNAs) are considered potential biomarkers for cancer diagnosis and prognosis irrespective of tumor stage and mutations[2]. Among all miRNAs used as biomarkers, mir-142 has a significant role in modulating oncogenic molecules [3]. Bioinformatics studies proposed the role of mir-142 in regulating the expression of key genes [4]. A very prominent finding about miR-142 and other miRNAs is that elevated miRNA levels were exclusively

observed in the group of high-risk patients. During embryonic development, homeostasis, and disease progression, miR-142, a single-stranded RNA that is processed from hairpin transcripts, acts as an effective regulator of many cellular processes and related signaling pathways.

The gene encoding miR-142 is located on the human chromosome 17q22. Pre-miRNA, an arm packet that is processed during the miRNA biogenesis, generates miR-142-3p and miR-142-5p, distinguishes the different sequences of miR-142-3p and miR-142-5p, and determines a different goal for each one. In other words, miR-142-3p, is located in the structure of the stem-loop on the 3′ arm, while miR-142-5p is located on the 5′ arm. Based on the studies on mesenchymal and hematopoietic cells, it was indicated that transcription start site and proximal polyadenylation site were located at −1205 and +431, respectively, and miR-142 is expected to have a length of 1,636 nucleotides [5-7]. The aberrant expression of miR-142-3p and miR-142-5p has been found in multiple solid cancers (Figure 1). Numerous efforts have been made to develop novel diagnostic biomarkers for various cancers because of aggressiveness and low sensitivity of cancer screening methods. In this review, we summarize some molecular mechanisms and the expression status of miRNA-142 function in the pathogenesis of various cancers.

2 The role of miR-142 in lung cancer

Lung cancer, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), are dangerous cancers, especially in males[8]. They are considered environmental-induced diseases owing to the high risk of exposure to tobacco smoke [9]. NSCLC, accounts for approximately 80% of lung cancer cases, is divided mainly into three subtypes: lung adenocarcinoma (LUAD), squamous cell carcinoma (LUSQ), and large cell carcinoma. MiR-142-5p was significantly downregulated in NSCLC tissues and cell lines compared to normal human lung tissues. Previous studies showed that PIK3CA was a potential target of miR-142-5p, and expression reduction of PIK3CA by miR-142-5p resulted in the suppression of PI3K/Akt pathway [3]. Accounting to studies on miR-142-3p levels and tumor stages, there were differences between pulmonary adenocarcinoma patients with low and high risk for recurrence [10]. MiR-142-3p was downregulated in NSCLC tissues as well as in cell lines and therefore, inducing the overexpression of miR-142-3p may inhibit NSCLC cell proliferation and apoptosis. Evidence showed HMGB1 acted as a target for miR-142-3p in NSCLC-affected cells that was confirmed by luciferase reporter assay, which confirmed the existence of target specificity between miR-142-3p and HMGB1 3'-untranslated region [11]. In fact, miR-142 may play prominent roles in lung cancer via some pathways, depending on transient receptor potential (TRP) ion channels [12]. Transient receptor potential ankyrin 1 (TRPA1), as an ion channel, is implicated in lung adenocarcinoma (LUAD), where its roles and mechanisms of

action remain unknown. We know that the members of TRP channel superfamily consist of a general tetrameric six-transmembrane (S1-S6) and likely a similar mechanism of pore-opening in architecture, which TRPA1 is activated by different electrophilic chemicals and oxidants to play a role in cells [12, 13]. It seems the interaction of TRAP1 with different molecules such as Notch1 plays important roles in cell signaling. TRPA1 contains 16 ankyrin repeats in N-terminal region with a putative, yet unknown, role in pore-gating and mediating protein–protein interactions, where the binding partners remain to be identified. On the other hand, in lung malignancies, especially LUAD, many studies have previously shown that the membrane receptor of fibroblast growth factor receptor 2 (FGFR2) is a critical driver of disease progression, especially under non-stimulated conditions [14, 15]. Since the constitutive activation of kinase domain has been defined in patients with LUAD, inhibition of this receptor may be considered a great therapeutic target [16]. However, a highly effective method for targeting FGFR2 has not yet been introduced. In addition, TRPA1-FGFR2 provides the oncogenic process in LUAD and its metastasis to the brain. Berroute et al. demonstrated that TRPA1 was decreased in LUAD cells, which inhibited FGFR2- driven cellular proliferation and invasion [17]. They also unraveled the relationship of astrocyte with LUAD cells, which occurred by the transfer of TRPA1-targeting exosomes containing miRNA-142-3p from astrocytes to LUAD. It was already demonstrated that the astrocyte-

secreted miRNAs were involved in depleting the expression of proteins in the brain niche [18, 19]. In addition, these circulating miRNAs are known to be transported as cargo in cell-derived vesicles called exosomes to mediate cellular communication and function [20]. According to these findings, miR-142-3p can regulate TRPA1 at mRNA level. This finding corroborates the finding that shows the level of miR-142 is reduced in lung cancers. Based on previous reports, there is a crosstalk between cancer cells and astrocytes in the brain [20], which modulates protein expression in tumor cells [21]. So we postulate that the release of chemokines by cancer cells can attract astrocytes and induce the release of exosomal miRNAs [19]. Therefore, the measurement of exosomal miRNAs in the bloodstream may indicate the prognosis to choose a better treatment strategy.

3 miR-142 roles in breast cancer

Breast cancer is the most common form of cancer among women, which remains to be challenging worldwide[22]. MiR-142 has been identified to act as a BC tumor suppressor. The critical role of miR-142-5p has been demonstrated in various cancers, its underlying mechanisms need further elucidation. Overexpressed miR-142-5p and Sorbin and H3 domain-containing protein (SORBS1) induced the proliferation, invasion, and migration of BC cells, thereby suggesting the inhibition of miR-142-5p may silence SORBS1. MiR-142-5p regulates SORBS1 as a critical

modulator of BC development; thus it may a promising candidate for therapeutic approaches [23]. Moreover, the increased miR-142-3p expression repressed BC cell line development and metastasis through *in vitro* and *in vivo* gain-of-function assays. Further, miR-142-3p may moderate the protein-level expression of Ras-related C3 botulinum toxin substrate 1 (RAC1), which concurrently reduces the level of epithelial-to-mesenchymal transition (EMT) protein, activity of serine/threonine-protein kinase (PAK1) phosphorylation, suppression of the expression of oncogene High Mobility Group AT-Hook 1 (HMGA1) and Frizzled Class Receptor 7 (FZD7), and cytoskeleton reorganization. Studies reported that miR-142-3p has an inhibitor role in cell proliferation, migration, invasion, and metastasis [24, 25]. Mir-142-3p, which downregulates the stem cell and radio-resistance characteristics of BC, is regulated by a reduced function of β-catenin in BC cells. Thus, miR-142-3p can help target cancer stem cells [26]. In this regard, miR-142-3p may be suggested for diagnosis, early detection, and treatment of BC.

It was established that miR-142-3p regulated drug resistance in BC, but its molecular pathway involved remains unclear. For example, miR-142-3p was dramatically increased doxorubicin (DOX) sensitivity and DOX-induced apoptosis in DOX-resistant MCF-7 cell line (MCF-7/DOX) via downregulating high-mobility group box 1 (HMGB1) expression [2, 27].

In ER-positive BC cells, estrogen receptor 1 (ER1) prevents apoptosis via AKT activation. Consequently, miR-142-3p can promote apoptosis via decreasing the activity of ESR1 and AKT by increasing pro-apoptotic caspase-9 and caspase-3 levels, while at the same time inhibiting anti-apoptotic Bcl-2 levels. There are pieces of evidence about the involvement of anti-apoptotic mechanisms in many cancers as well as some autoimmune diseases [28, 29]. It was also demonstrated that the stemness of ER-positive BC correlated with downregulation of mRNA levels in various cancer stem cell markers, including CD44, CD133, ALDH, Sox2, and Nanog by inducing miR-142-3p. Moreover, colony formation assay indicated that restoration of the expression of miR-142-3p in miR-142-3p-transfected cells reduced cancer stem cell properties in ER-positive BC cells (Figure 2) [30].

4. The role of miR-142 in gynecological malignancies

4.1. The role of miR-142 in prostate cancer

MiR-142-3p acts as an oncogene by targeting Forkhead box transcription factor O1 (FOXO1) in prostate cancer. FOXO1 works as a tumor suppressor protein in several cancers, especially prostate cancer. FOXO1 induces cell cycle arrest in G0/G1 phases, elevates P21 and cyclin D expression. Therefore, FOXO1 regulates cellular proliferation and cell cycle progression. MiR-142-3p negatively regulates FOXO1 expression by targeting the 3′-UTR region of FOXO1 mRNA [31]. Barceló et.al

showed the expression level of miR-142-3p and miR-142-5p was unregulated in semen samples in patients with prostate cancer. Therefore, the expression level of miR-142 beside PSA level could be considered diagnostic/prognostic biomarker for prostate cancer [32].

4.2. The role of miR-142 in endometrial cancer

Mir-142 plays a different role in various cancers. MiR-142 acts as a tumor suppressor in endometrial cancer. Mir-142 targets the 3′-UTR region of cyclin-D and inhibits its expression. Also, the high expression of Cyclin-D is associated with poor survival in endometrial cancer. MiR-142 repressed the tumor growth by downregulation of Ki-67 and Cyclin-D expression in endometrial cancer mouse models [33]. The expression level of miR-142 is a reliable prognostic biomarker for therapy response and survival in endometrial cancer. Recent studies showed the survival rate in patients with a high expression level of miR-142 is better than patients with high expression levels of mir-4758/mir-876 [34, 35].

4.3. **The role of miR-142 in cervical cancer**

The expression level of miR-142-3p is downregulated in cervical cancer and the low expression of miR-142 is associated with poor prognosis in cervical cancer [36]. MiR142-3p targets the 3′-UTR region of Frizzled7 receptor (FZD7) and suppressed the cellular proliferation and invasion of cervical cancer. FZD7 regulates cellular

proliferation and invasion through activating of Wnt-β-catenin signaling pathway. Downregulation of FZD7 induces the overexpression of E-cadherin [37]. Also, miR-142-3p induces the expression of E-cadherin and inhibits the expression of snail, which indicates to the negative regulation of epithelial-mesenchymal transition (EMT) in cervical cancer [38]. Jiang et.al showed that miR-142 suppresses the proliferation of cervical cancer cells via targetingHMGB1. HMGB1 regulates carcinogenesis via activating cellular migration and metastasis through EMT in cervical cancer. Moreover, HMGB1 promotes cancer cell proliferation by regulating ERK-MAPK and PI3K/Akt signaling pathways [39, 40].

4.4. The role of miR-142 in ovarian cancer

MiR-142-5p is one of microRNAs, which has a diagnostic value in ovarian cancer [41]. X. et al. study showed that the expression level of miR-142-3p is upregulated in sera of patients with ovarian cancer and its expression level negatively correlates with a pathological grade in cancer [42]. Findings indicated that MiR-142-5p was downregulated in ovarian cancer cells. The overexpression of KCNQ1OT1 (a long non-coding RNA gene) promotes the growth and invasion of ovarian cancer cells through MIR-142-5p /calpain 10 (a calcium-dependent cysteine protease) pathway [43]. Also, miR-142-5p enhances ovarian cancer cells' sensitivity to cisplatin chemotherapy by targeting X-linked inhibitor of apoptosis (XIAP) 3′-UTR and several anti-apoptotic genes like baculoviral IAP repeat-containing 3 (BIRC3), B-

cell lymphoma-2 (BCL2), BCL2-like 2 (BCL2L2), and myeloid cell leukemia sequence 1 (MCL1) [44].

MiR-142-3p negatively regulates Sirtuin 1 (SIRT1) expression by targeting the 3′-UTR region of it in ovarian cancer cells [45]. SIRT1 enhances the cell growth, chemoresistance and invasiveness of ovarian cancer cells via suppression of oxidative stress [46]. MiR-142-3p plays a tumor-suppressor role in ovarian cancer and inhibits cancer cell growth and chemoresistance through targeting SIRT1 [45].

5 The role of miRNA-142 in colon cancer

The third most prevalent cancer is colon cancer, which significantly causes cancer mortality and genetic factors in addition to environmental factors contribute to the development of malignancy in this organ [47]. New molecular techniques for the identification of colon cancer are now being tested; however, several of these techniques should be validated in broad, randomized studies prior the clinical usage [48, 49]. The molecular pathways underlying the pathogenesis of colon cancer are still poorly known. Several pieces of evidence demonstrated miRNAs play significant roles in launching, progressing, and developing colon cancer [50, 51].

MiR-142-3p has been contributed to the regulation of inflammatory and immune responses such as development and function of T cells and the expression of LPS-induced interleukin-6 (IL-6) [52, 53]. Since inflammation plays a substantial role in

colon carcinogenesis, researchers utilized three algorithmic programs to investigate anti-inflammatory function of miR-142-3p to predict the potential of its target genes. MiR-142-3p is downregulated in colorectal cancer (CRC) as a tumor suppressor. Moreover, IRAK1 might be a target gene for miR-142-3p [54]. IRAK1 belongs to the family of interleukin-1 receptor-activated kinases (IRAKs) and is a significant component of the IL-1R/TLR signal transduction [55]. IL-1R/TLR stimulates the development of a receptor complex upon ligand binding that recruits myeloid differentiation factor 88 (MyD88) and IRAK1; thereby, initiating a cascade of downstream signaling, which ultimately results in NF-κB activation and the induction of expression of inflammatory target genes. Therefore, Gottipati et al. focused on characterizing IRAK1 as a potential miR-142-3p target in CRC cells and findings indicated that miR-142-3p directly suppressed IRAK1, thereby inhibiting its expression at both mRNA and protein levels [55]. This research also exhibited that miR-142-3p suppressed the activation of the NF-κB signal caused by LPS in CRC cells, thus decreasing the expression of inflammatory cytokines, including IL-6, IL-8, MCP-1, CCL5, and CSF-1. Therefore, it was indicated that miR-142-3p was a crucial element in regulating NF-κB activation, and its anti-inflammatory function may relate to the suppression of CRC carcinogenesis [54].

In recent decades, scientists have discovered that the advancement of CRC is accelerated by the expression of some biomarkers, e.g., CD133, leucine-rich-repeat-

containing G-protein-coupled receptor 5 (Lgr5), and ATP binding cassette (ABC) G2. The elevated expression of CD133, Lgr5 and ABCG2 genes enhances the proliferation and drug resistance ability in cancer cells such as colon cancer [56-58]. It has been established that miR-142-3p can downregulate the endogenous and exogenous expression of CD133, Lgr5, and ABCG2 by binding to their 3′-UTRs and coding sequences. Further, miR-142-3p levels negatively correlate with the expression of CD133, Lgr5, and ABCG2 and tumor size, while positively correlate with differentiation in colon cancers. When miR-142-3p is transfected into colon cancer cells, it induces downregulation of the Cycline-D1, thereby causing the G1 phase cell cycle arrest and elevating the susceptibility of the cells to 5-fluorouracil. Additionally, miR-142-3p, which was repressed by OCT4 and hypomethylation of its promoter, correlated with a decreased miR-142-3p. Such findings may reveal a novel pathway of molecular mechanisms and propose a possible therapeutic strategy for colon cancer treatment [59].

Gao et al. evaluated the targets of miR-142-3p that its potential target genes were predicted for research using software and network methods, and RAC1 was recognized as a target for miR-142-3p among candidate target genes. RAC1 belongs to the Rho family of GTPases that may result from tumor development via the NF-κB signaling pathway, and GTPRAC1 can bind specifically to Bcl-2 to induce anti-apoptotic cell reactions and regulate tumor angiogenesis [60].

RAC1 was substantially increased in SW480 cells transfected with miR-142-3p expression plasmid and had a direct relationship with tumor size and metastasis. These results show the impact of miR-142-3p on proliferation and invasion in CRC cells by increasing RAC1 expression [61].

Zhu et al. showed that miR-142-3p was downregulated in 78.4% (91/116) of the primary CRC tissues compared to adjacent non-tumor tissues. They also discovered that miR-142-3p mimics decreased *in vitro* cell viability and colony development by inducing cell cycle suspension in CRC-derived cells and inhibited *in vivo* tumor cell growth in xenografted nude mice. Predictions and dual-luciferase reporter assays identified CDK4 as a possible target of miR-142-3p, and it was found that miR-142-3p mimics and inhibitors could reduce and elevate CDK4 protein levels in CRC-derived cells, respectively. CDK4/CDK6 is associated with a complex of cyclins that can regulate the transition of the G1/S phase cell cycle and prevent Rb binding to E2F. Hence, miR-142-3p may be involved in the cell cycle arrest in CRC cells through CDK/pRb/E2F pathway, however, it needs further investigation [62].

The serum analysis of 363 patients with CRC and 156 healthy controls was evaluated by Gao et al. In CRC patients, miR-142-3p serum levels were significantly lower than healthy controls. A low serum level of miR-142-3p has been remarkably associated with advanced CRC. Survival analysis revealed that patients with a low serum level of miR-142-3p were lower overall 5 years survival rate than patients

with a high serum miR-142-3p level (67.4% vs. 76.9%) [63]. Based on these findings, it was suggested that miR-142-3p should be used for the evaluation and optimal risk stratification of patients with CRC. In addition, serum miR-142-3p may be a promising biomarker for postoperative prognosis of patients with CRC [63, 64]. On the other hand, miR-142-3p could be engaged in the control of cancer cell proliferation and CRC metastasis through mechanisms, including targeting the transcription factor 7 (TCF-7), fatty acid synthase (FASN), and oncogene MYC pathway [63] [65].

Despite a single miRNA's high diagnostic potential for detecting CRC, a panel of miRNA biomarkers can enhance the accuracy of early diagnosis of this malignancy. A panel of 8 miRNAs (miRNA-532-3p, miRNA-331, miRNA-195, miRNA-17, miRNA-142-3p, miRNA-15b, miRNA-532, and miRNA-652) was examined by Kanaan et al. that could distinguish patients with colorectal adenomas from healthy controls [66]. Patients with advanced colorectal adenoma were also differentiated by a panel containing 5 miRNAs (miRNA-331, miRNA-15b, miRNA-21, miRNA-142-3p, and miRNA-339-3p) [67].

According to studies, substantial overexpression of miR-142-5p was revealed in cancer cell lines and colorectal cancer tissues, respectively. Additionally, patients with colorectal cancer who express an elevated miR-142-5p level, have a poor prognosis compared with those who had a reduced miR-142-5p expression level.

Then, the modulation of multiple predictive targets of miR-142-5p such as FAM134B, KLF6, EPAS1, and KRAS was investigated utilizing bioinformatics methods miRDB and miRbase [68, 69]. In miR-142-5p overexpressing (SW480+miR-142 and SW48+miR-142) cells, a substantial reduction in Kruppel-like factor 6 (KLF6) detected compared with control group. On the other hand, inhibition of endogenous miR-142-5p, by treatment with anti-miR-142-5p, induced substantial upregulation of KLF6 expression. Hence, KLF6 could be effective to establish successful therapeutic strategies for colon cancer cells by targeting miRNAs like miR-142-5p for KLF6 overexpression [69].

Using starBase v2.0, Liu et al. indicated that succinate dehydrogenase-B (SDHB) was a possible target of miR-142-5p, while SDHB was negatively associated with the growth of cancer by controlling energy metabolism. Then, transfection experiment and luciferase assay were conducted for the identification of the relationship between miR-142-5p and SDHB in CRC tissues and cell lines. The results revealed that miR-142-5p was upregulated in CRC but SDHB was downregulated and verified as miR-142-5 target. Depletion of SDHB through miR-142-5p upregulation suppressed oxygen intake from CRC cells; meanwhile, enhanced glucose consumption and production of lactate [70]. According to previous studies, loss of SDHB through miR-142-5p upregulation promotes metabolic switching from oxidative phosphorylation to aerobic glycolysis in CRC,

which supports rapid growth and proliferation of CRC [70]. This impact of miR-142-5p was abrogated by SDHB overexpression, which showed that SDHB depletion mediates tumor-promoting activities of miR-142-5p. Immunohistochemistry assay also indicated that staining of Cyclin-D1 and Ki67 was declined by miR-142-5p inhibitors in xenografted tumors, and knocking down SDHB repressed the reduction of the staining. Thus, SDHB is a possible future molecular therapeutic component, which may be a promising candidate for therapies [70].

Shi et al. declared that miR-142-5p could be served as a potential tumor suppressor in CRC and was upregulated in tumor tissues after transcatheter arterial infusion chemotherapy (TAI), suggesting its potential clinical prominence for evaluating the functionality of TAI and predicting CRC progress. Therefore, the findings indicated that miR-142-5p could specifically bind to the 3′-UTR of the endothelial PAS domain protein 1 (EPAS1), a common endothelial-cell transcription factor and decrease its expression; thus, EPAS1 may be proposed as a possible target for cancer therapy [71].

6 MiR-142 roles in colorectal cancer

Aberrant expression of miR-142, either miR-142-3p or miR-142-5p, in colorectal cancer cells and tissue samples has been reported in several studies with paradoxical

implications. Chen *at al*. investigated the expression profile of microRNAs in human colorectal cancer by miRNA microarray. They found the significant upregulation of miR-142-3p in colorectal cancer tissues, which were associated with clinic-pathological features compared with matched non-tumor tissues [72]. Zhou *et al*., using quantitative real-time PCR (qRT-PCR) confirmed that miR-142-3p was significantly upregulated in 60 samples of three kinds of colorectal cancer cell lines [65]. To identify the most important circulating microRNAs in plasma of patients with colorectal cancer. Ghanbari *et al.* performed microRNA microarray on 37 patients with colorectal cancer and 8 healthy controls and reported miR-142-3p as one of the significantly downregulated microRNAs in colorectal cancer tissues. This study suggested miR-142-3p as a potential diagnostic biomarker for patients with CRC [64]. Zhu *et al*. demonstrated the aberrant expression of miR-142-3p in 116 primary CRC samples and adjacent non-tumor tissues. They found that miR-142-3p was downregulated in 78.4% (91/116) of the primary CRC tissues compared to control [62]. In a recent study, Gao *et al*. evaluated serum miR-142-3p level in 363 patients with CRC and 156 healthy controls to evaluate miR-142-3p as a serum marker in patients with CRC that showed a significantly lower level of miR-142-3p in patients with CRC than healthy controls. Also, the study of the correlation between serum miR-142-3p levels and survival outcomes revealed the association between low serum miR-142-3p levels with an advanced stage of tumor and lower

5-year overall survival rate. So, serum miR-142-3p was suggested as a diagnostic and prognostic marker for CRC [73].

Vychytilova-Faltejskova *et al*. revealed that the expression of miR-142-5p in 427 samples from CRC patients was significantly elevated in CRC tissues compared to controls [74]. The study performed by Yin *et al*. demonstrated the overexpression of miR-142-5p in 15 CRC tissue samples [75], whereas Shi *et al*. declared the downregulation of miR-142-5p in 80 CRC tissue samples in stage III compared to adjacent normal tissues [71]. Also, Liu *at al*. showed the expression of miR-142-5p was upregulated in CRC tissue samples compared to healthy controls by qPCR [70]. Islam *et al*. examined the expression of miR-142-5p in 125 CRC tissue samples and cell lines and found it was significantly elevated in 72% of them compared to control. Moreover, they reported that miR-142-5p was associated with clinicopathologic factors, including sites of cancer B-Raf mutation. Patients with CRC who expressed an elevated level of miR-142-5p showed poor prognosis in comparison to those who expressed a low level of miR-142-5p [69]. In addition, they revealed that cancers related to proximal and distal colorectum present a significant difference in miR-142-5p overexpression profile [69], which may be the result of different physiological, biochemical make-up and finally, differential gene expression patterns [76]. This implies the different roles of miR-142-5p in different pathological sites of CRC. The differential expression of miR-142-5p in the proximal and distal

sites of the colorectum implied its role in colorectal cancer pathogenesis could be tissue-specific and might target genes in these locations differently [69].

Mechanism of action of miR-142 in colorectal carcinomas

Growth-promoting or oncogenic features of miR-142 in colorectal carcinomas have been reported in several publications. Also, different mechanisms have been suggested for miR-142-mediated tumorigenesis in CRC. Gao et al. study confirmed the oncogenic function of miR-142-3p in CRC, as downregulation of miR-142-3p significantly decreased cell migration and invasion [61]. In this study, colorectal cancer SW480 cells transfected with miR-142-3p expression plasmid showed an upregulated level of RAC1 and decreased invasiveness of cells. Inversely, cells transfected with miR-142-3p silencer plasmids showed a decreased level of RAC-1. The researchers suggested the indirect regulation of RAC1 by miR-142-3p [61]. To understand the tumorigenesis mechanisms of miR-142-3p, Zhu *et al.* evaluated the consequences of miR-142-3p up- or downregulation in CRC-derived cells *in vitro* and *in vivo*. The experiments on miR-142-3p up-regulation showed that cell cycle arrest resulted in reduced cell viability and colony formation, which further confirmed by inhibition of tumor cell growth in xenografted nude mice. Inversely, the experiments with miR-142-3p inhibitor caused an increase in viability and colony-forming capacity of cells and tumor cell growth in xenografted nude mice

[62]. Moreover, they reported that CDK4, as a potential miR-142-3p target, may be reduced by miR-142-3p mimics, whereas increased by miR-142-3p inhibitors in CRC-derived cells [62]. As another target for miR-142-3p, RAC1 was identified by Gao *et al*. in SW480 cell lines. In this study, by activating RAC1, miR-142-3p increased cellular invasion in colorectal cancer cells. The elevated expression of RAC1 was significantly associated with higher tumor stage and metastasis [61]. In a study by Zhou *et al*., transcription factor 7 (T-cell specific, HMG box; TCF7) (*TCF7)* was predicted and identified as a target for miR-142-3p. *TCF7* was post-transcriptionally and negatively downregulated by miR-142-3p. *TCF7* mRNA and protein are upregulated in colorectal cancer tissues and colorectal cancer cell lines, indicating its function as an oncogene in promoting tumor cell proliferation and inhibiting apoptosis. Further experiments on SW480 colorectal cancer cells demonstrated that the overexpression of miR-142-3p could potently inhibit cell proliferation by inhibiting TCF7 expression. So, these results showed the miR-142-3p, with *TCF7* as a direct target, may be involved in the regulation of cell proliferation in colorectal cancer [65].

Liu *at al*. suggested succinate dehydrogenase-B (SDHB) as a candidate target for miR-142-5p. The study demonstrated the up-regulation of miR-142-5p, while down-regulation of SDHB in CRC. The decrease in SDHB was the result of abnormal upregulation of miR-142-5p in CRC; however, confirmed SDHB as a target for miR-

142-5p. SDHB exerts negative effects on cancer development by regulation of energetic metabolism. This is mediated by oxygen intake inhibition of CRC cells, but increased glucose consumption and lactate production; thereby facilitating generation of aerobic glycolysis. On the other hand, it has been demonstrated that miR-142-5p has positive roles in growth, proliferation, and colony formation of CRC, but inhibits apoptosis in these cells. SDHB overexpression evokes these effects of miR-142-5p, which indicates that miR-142-5p mediated its tumor-promoting functions through SDHB depletion [70]. In a study, among several targets predicted for miR-142-5p, including FAM134B, KLF6, EPAS1, and KRAS, only KLF6, which is a tumor suppressor, showed a significant reduction in miR-142-5p-overexpressing cells. Inversely, inhibition of endogenous miR-142-5p resulted in significant upregulation of KLF6. Also, overexpression of miR-142-5p promoted cell proliferation, colony formation, and wound healing capacities, while decreased cancer growth properties following the inhibition of endogenous miR-142-5p. These effects were mediated through the modulation of KLF6. As the expression of miR-142-5p and KLF6 protein are inversely correlated in colon cancer cells [69].

Because of B-Raf contribution to the pathogenesis of CRC [77], Islam *et al*. evaluated its association with miR-142-5p expression and found that miR-142-5p could contribute to the tumorigenesis by modulating the expression of B-Raf as either directly or indirectly [69].

7 Conclusion

In summary, miR-142-5p expression is important in predicting molecular progression, tumor growth, and patient prognosis in several carcinomas and exerts its oncogenic properties *in vitro* by targeting special proteins and molecules, which could be a tumor suppressor in regulating of growth, proliferation, apoptosis, and colony formation of cancer cells. Novel insight is provided into the cancer development regulated by miR-142, which can serve as a non-invasive biomarker in cancer prognosis, diagnosis. MiR-142 could also be a potential target of therapy in future molecular medicine; however, further studies are needed to confirm it.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Author contributions

Y. P. contributed to design and writing the paper. M. M., E. D., Z, P., and S. R. contributed to data collection, writing the paper, and providing the tables. K. N. contributed to designing the paper, revising, and analyzing the final version of the manuscript.

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References

[1] Seijo, L.M., et al., *Biomarkers in Lung Cancer Screening: Achievements, Promises, and Challenges.* J Thorac Oncol, 2019. **14**(3): p. 343-357.

[2] Moghadasi, M., et al., *Emerging molecular functions of microRNA-124: Cancer pathology and therapeutic implications.* Pathology-Research and Practice, 2020. **216**(3): p. 152827.

[3] Xue, J., et al., *Dickkopf-1 Is a Biomarker for Systemic Lupus Erythematosus and Active Lupus Nephritis.* Journal of immunology research, 2017. **2017**.

[4] Muro, Y., et al., *Brief Report: autoantibodies to DNA mismatch repair enzymes in polymyositis/dermatomyositis and other autoimmune diseases: a possible marker of favorable prognosis.* Arthritis & Rheumatology, 2014. **66**(12): p. 3457-3462.

[5] Fabian, M.R., N. Sonenberg, and W. Filipowicz, *Regulation of mRNA translation and stability by microRNAs.* Annual review of biochemistry, 2010. **79**: p. 351-379.

[6] Bartel, D.P., *MicroRNAs: target recognition and regulatory functions.* cell, 2009. **136**(2): p. 215-233.

[7] Ataollahi, M., et al., *Breast cancer and associated factors: a review.* Journal of medicine and life, 2015. **8**(Spec Iss 4): p. 6.

[8] Zohre, S., et al., *Trichostatin A-induced apoptosis is mediated by Kruppel-like factor 4 in ovarian and lung cancer.* Asian Pacific Journal of Cancer Prevention, 2014. **15**(16): p. 6581-6586.

[9] Jemal, A., et al., *Global cancer statistics.* CA Cancer J Clin, 2011. **61**(2): p. 69-90.

[10] Kaduthanam, S., et al., *Serum miR-142-3p is associated with early relapse in operable lung adenocarcinoma patients.* Lung Cancer, 2013. **80**(2): p. 223-7.

[11] Altieri, D.C., *Validating survivin as a cancer therapeutic target.* Nature Reviews Cancer, 2003. **3**(1): p. 46.

[12] Meents, J.E., C.I. Ciotu, and M.J.M. Fischer, *TRPA1: a molecular view.* J Neurophysiol, 2019. **121**(2): p. 427-443.

[13] Nilius, B., J. Prenen, and G. Owsianik, *Irritating channels: the case of TRPA1.* J Physiol, 2011. **589**(Pt 7): p. 1543-9.

[14] Dabrowski, A. and H. Umemori, *Buttressing a balanced brain: Target-derived FGF signaling regulates excitatory/inhibitory tone and adult neurogenesis within the maturating hippocampal network.* Neurogenesis (Austin), 2016. **3**(1): p. e1168504.

[15] Campbell, A.W., *Autoimmunity and the gut.* Autoimmune diseases, 2014. **2014**.

[16] Hynkova, A., et al., *N-terminal tetrapeptide T/SPLH motifs contribute to multimodal activation of human TRPA1 channel.* Sci Rep, 2016. **6**: p. 28700.

[17] Berrout, J., et al., *TRPA1-FGFR2 binding event is a regulatory oncogenic driver modulated by miRNA-142-3p.* Nat Commun, 2017. **8**(1): p. 947.

[18] Tanaka, K., et al., *Expression of survivin and its relationship to loss of apoptosis in breast carcinomas.* Clinical Cancer Research, 2000. **6**(1): p. 127-134.

[19] Wang, W., E.J. Kwon, and L.H. Tsai, *MicroRNAs in learning, memory, and neurological diseases.* Learn Mem, 2012. **19**(9): p. 359-68.

[20] Birks, D.K., et al., *Survey of MicroRNA expression in pediatric brain tumors.* Pediatr Blood Cancer, 2011. **56**(2): p. 211-6.

[21] Zhang, L., et al., *Microenvironment-induced PTEN loss by exosomal microRNA primes brain metastasis outgrowth.* Nature, 2015. **527**(7576): p. 100-104.

[22] Nejati-Koshki, K., A. Akbarzadeh, and M. Pourhassan-Moghaddam, *Curcumin inhibits leptin gene expression and secretion in breast cancer cells by estrogen receptors.* Cancer cell international, 2014. **14**(1): p. 1-7.

[23] Yu, W., et al., *MiR-142-5p Acts as a Significant Regulator Through Promoting Proliferation, Invasion, and Migration in Breast Cancer Modulated by Targeting SORBS1.* Technology in Cancer Research & Treatment, 2019. **18**: p. 1533033819892264.
[24] Heasman, S.J. and A.J. Ridley, *Mammalian Rho GTPases: new insights into their functions from in vivo studies.* Nature reviews Molecular cell biology, 2008. **9**(9): p. 690-701.
[25] Hoang, M.V., J.A. Nagy, and D.R. Senger, *Active Rac1 improves pathologic VEGF neovessel architecture and reduces vascular leak: mechanistic similarities with angiopoietin-1.* Blood, The Journal of the American Society of Hematology, 2011. **117**(5): p. 1751-1760.
[26] Troschel, F.M., et al., *miR-142-3p attenuates breast cancer stem cell characteristics and decreases radioresistance in vitro.* Tumor Biology, 2018. **40**(8): p. 1010428318791887.
[27] Liang, L., et al., *MiR-142-3p enhances chemosensitivity of breast cancer cells and inhibits autophagy by targeting HMGB1.* Acta Pharmaceutica Sinica B, 2019.
[28] Pahlavan, Y., et al., *Survivin modulatory role in autoimmune and autoinflammatory diseases.* Journal of cellular physiology, 2019. **234**(11): p. 19440-19450.
[29] Pahlavan, Y., et al., *Phosphorylation Modulates Survivin Function in Behcet's Disease.* Advanced Pharmaceutical Bulletin, 2020. **10**(2): p. 278-283.
[30] Mansoori, B., et al., *miR-142-3p is a tumor suppressor that inhibits estrogen receptor expression in ER-positive breast cancer.* Journal of Cellular Physiology, 2019. **234**(9): p. 16043-16053.
[31] Tan, Y.-F., et al., *MiR-142-3p functions as an oncogene in prostate cancer by targeting FOXO1.* Journal of Cancer, 2020. **11**(6): p. 1614.
[32] Barceló, M., et al., *Semen miRnAs contained in exosomes as non-invasive Biomarkers for prostate cancer Diagnosis.* Scientific reports, 2019. **9**(1): p. 1-16.
[33] Su, Y., et al., *miR-142 suppresses endometrial cancer proliferation in vitro and in vivo by targeting cyclin D1.* DNA and cell biology, 2019. **38**(2): p. 144-150.
[34] Wu, Y.-S., et al., *A four-miRNA signature as a novel biomarker for predicting survival in endometrial cancer.* Gene, 2019. **697**: p. 86-93.
[35] Jayaraman, M., et al., *Identification of novel diagnostic and prognostic miRNA signatures in endometrial cancer.* Genes & cancer, 2017. **8**(5-6): p. 566.
[36] Li, M., et al., *Expression of microRNA-142-3p in cervical cancer and its correlation with prognosis.* Eur Rev Med Pharmacol Sci, 2017. **21**(10): p. 2346-2350.
[37] Liu, B., et al., *Effect of microRNA-27b on cisplatin chemotherapy sensitivity of oral squamous cell carcinoma via FZD7 signaling pathway.* Oncology letters, 2019. **18**(1): p. 667-673.
[38] Deng, B., et al., *MicroRNA-142-3p inhibits cell proliferation and invasion of cervical cancer cells by targeting FZD7.* Tumor Biology, 2015. **36**(10): p. 8065-8073.
[39] Jiang, D., et al., *MiR-142 inhibits the development of cervical cancer by targeting HMGB1.* Oncotarget, 2017. **8**(3): p. 4001.
[40] Wu, L. and L. Yang, *The function and mechanism of HMGB1 in lung cancer and its potential therapeutic implications.* Oncology letters, 2018. **15**(5): p. 6799-6805.
[41] Wiczling, P., et al., *Bayesian multilevel model of micro RNA levels in ovarian-cancer and healthy subjects.* PloS one, 2019. **14**(8).
[42] Wu, X., et al., *Elevated levels of dendritic cell-correlated miRNAs in ascites and sera of patients with ovarian cancer.* Xi bao yu fen zi mian yi xue za zhi= Chinese journal of cellular and molecular immunology, 2015. **31**(3): p. 383-386.
[43] Liu, H., et al., *KCNQ1OT1 promotes ovarian cancer progression via modulating MIR-142-5p/CAPN10 axis.* Molecular Genetics & Genomic Medicine, 2020: p. e1077.
[44] Li, X., et al., *miR-142-5p enhances cisplatin-induced apoptosis in ovarian cancer cells by targeting multiple anti-apoptotic genes.* Biochemical pharmacology, 2019. **161**: p. 98-112.

[45] Gao, J., et al., *MicroRNA-142-3p inhibits cell proliferation and chemoresistance in ovarian cancer via targeting sirtuin 1.* Experimental and therapeutic medicine, 2018. **15**(6): p. 5205-5214.
[46] Mvunta, D.H., et al., *SIRT1 regulates the chemoresistance and invasiveness of ovarian carcinoma cells.* Translational oncology, 2017. **10**(4): p. 621-631.
[47] Murphy, N., et al., *Lifestyle and dietary environmental factors in colorectal cancer susceptibility.* Molecular aspects of medicine, 2019.
[48] Loktionov, A., *Biomarkers for detecting colorectal cancer non-invasively: DNA, RNA or proteins?* World Journal of Gastrointestinal Oncology, 2020. **12**(2): p. 124.
[49] Shajari, E. and H. Mollasalehi, *Ribonucleic-acid-biomarker candidates for early-phase group detection of common cancers.* Genomics, 2020. **112**(1): p. 163-168.
[50] Zhu, K., et al., *Long non-coding RNA MBNL1-AS1 regulates proliferation, migration, and invasion of cancer stem cells in colon cancer by interacting with MYL9 via sponging microRNA-412-3p.* Clinics and Research in Hepatology and Gastroenterology, 2020. **44**(1): p. 101-114.
[51] Nishida, K., Y. Kuwano, and K. Rokutan, *The MicroRNA-23b/27b/24 Cluster Facilitates Colon Cancer Cell Migration by Targeting FOXP2.* Cancers, 2020. **12**(1): p. 174.
[52] Wang, X., et al., *MicroRNA-142-3p inhibits chondrocyte apoptosis and inflammation in osteoarthritis by targeting HMGB1.* Inflammation, 2016. **39**(5): p. 1718-1728.
[53] Sun, Y., et al., *Targeting of microRNA-142-3p in dendritic cells regulates endotoxin-induced mortality.* Blood, The Journal of the American Society of Hematology, 2011. **117**(23): p. 6172-6183.
[54] Zhiying, X., et al., *miR-142-3p inhibits LPS-induced activation of NF-κB by targeting IRAK1 in colorectal cancer.* Central European Journal of Immunology, 2013. **38**(4): p. 416-420.
[55] Gottipati, S., N.L. Rao, and W.-P. Fung-Leung, *IRAK1: a critical signaling mediator of innate immunity.* Cellular signalling, 2008. **20**(2): p. 269-276.
[56] Ricci-Vitiani, L., et al., *Identification and expansion of human colon-cancer-initiating cells.* Nature, 2007. **445**(7123): p. 111-115.
[57] Kobayashi, S., et al., *LGR5-positive colon cancer stem cells interconvert with drug-resistant LGR5-negative cells and are capable of tumor reconstitution.* Stem cells, 2012. **30**(12): p. 2631-2644.
[58] Zhu, M.M., et al., *Increased JNK1 signaling pathway is responsible for ABCG2-mediated multidrug resistance in human colon cancer.* Plos one, 2012. **7**(8).
[59] Shen, W.-W., et al., *MiR-142-3p functions as a tumor suppressor by targeting CD133, ABCG2, and Lgr5 in colon cancer cells.* Journal of molecular medicine, 2013. **91**(8): p. 989-1000.
[60] De, P., J.C. Aske, and N. Dey, *RAC1 Takes the Lead in Solid Tumors.* Cells, 2019. **8**(5): p. 382.
[61] Gao, X., et al., *MicroRNA-142-3p promotes cellular invasion of colorectal cancer cells by activation of RAC1.* Technology in cancer research & treatment, 2018. **17**: p. 1533033818790508.
[62] Zhu, X., et al., *miR-142-3p Suppresses Cell Growth by Targeting CDK4 in Colorectal Cancer.* Cellular Physiology and Biochemistry, 2018. **51**(4): p. 1969-1981.
[63] Gao, W., D. Pang, and S. Yu, *Serum level of miR-142-3p predicts prognostic outcome for colorectal cancer following curative resection.* Journal of International Medical Research, 2019. **47**(5): p. 2116-2125.
[64] Ghanbari, R., et al., *Downregulation of plasma MiR-142-3p and MiR-26a-5p in patients with colorectal carcinoma.* Iranian journal of cancer prevention, 2015. **8**(3).
[65] Zhou, J., et al., *MicroRNA-142-3p is frequently upregulated in colorectal cancer and may be involved in the regulation of cell proliferation.* Chinese science bulletin, 2013. **58**(23): p. 2836-2845.
[66] Kanaan, Z., et al., *A plasma microRNA panel for detection of colorectal adenomas: a step toward more precise screening for colorectal cancer.* Annals of surgery, 2013. **258**(3): p. 400-408.
[67] Giráldez, M.D., et al., *Circulating microRNAs as biomarkers of colorectal cancer: results from a genome-wide profiling and validation study.* Clinical gastroenterology and hepatology, 2013. **11**(6): p. 681-688. e3.

[68] Wong, N. and X. Wang, *miRDB: an online resource for microRNA target prediction and functional annotations.* Nucleic acids research, 2015. **43**(D1): p. D146-D152.
[69] Islam, F., et al., *MiR-142-5p act as an oncogenic microRNA in colorectal cancer: Clinicopathological and functional insights.* Experimental and molecular pathology, 2018. **104**(1): p. 98-107.
[70] Liu, S., et al., *miR-142-5p promotes development of colorectal cancer through targeting SDHB and facilitating generation of aerobic glycolysis.* Biomedicine & Pharmacotherapy, 2017. **92**: p. 1119-1127.
[71] Shi, D., et al., *Transcatheter arterial infusion chemotherapy increases expression level of miR-142-5p in stage III colorectal cancer.* Indian journal of cancer, 2015. **52**(6): p. 47.
[72] Chen, W., M. Lin, and J. Huang, *Clinical significance of aberrant microRNAs expression in human colorectal cancer.* World J Gastroenterol, 2010. **18**: p. 3187-3194.
[73] Gao, W., D. Pang, and S. Yu, *Serum level of miR-142-3p predicts prognostic outcome for colorectal cancer following curative resection.* 2019. **47**(5): p. 2116-2125.
[74] Vychytilova-Faltejskova, P., et al., *Serum-based microRNA signatures in early diagnosis and prognosis prediction of colon cancer.* Carcinogenesis, 2016. **37**(10): p. 941-950.
[75] Yin, Y., et al., *Systematic analysis of key miRNAs and related signaling pathways in colorectal tumorigenesis.* Gene, 2016. **578**(2): p. 177-184.
[76] Islam, F., et al., *MicroRNA-186-5p overexpression modulates colon cancer growth by repressing the expression of the FAM134B tumour inhibitor.* Experimental cell research, 2017. **357**(2): p. 260-270.
[77] Leslie, A., et al., *The colorectal adenoma–carcinoma sequence.* British Journal of Surgery, 2002. **89**(7): p. 845-860.

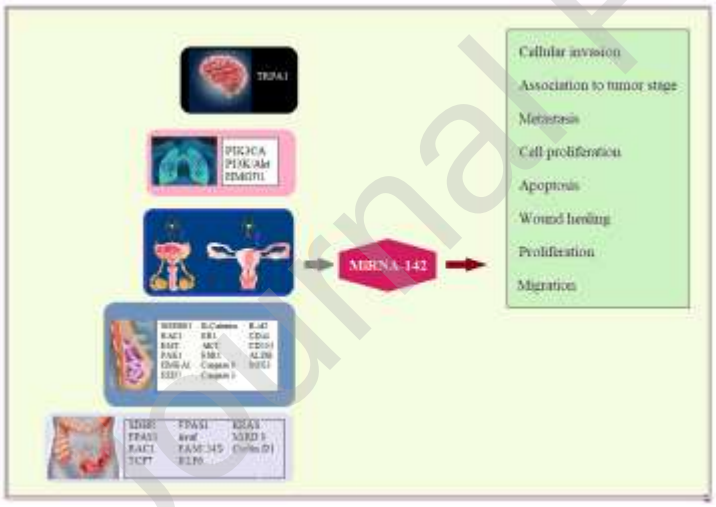

Figure 1. Emerging role of microRNA-142 in cancer. Mir-142 plays key roles in molecular mechanism and pathogenesis of various malignancies, including the brain, lung, genital system, breast and colon cancers.

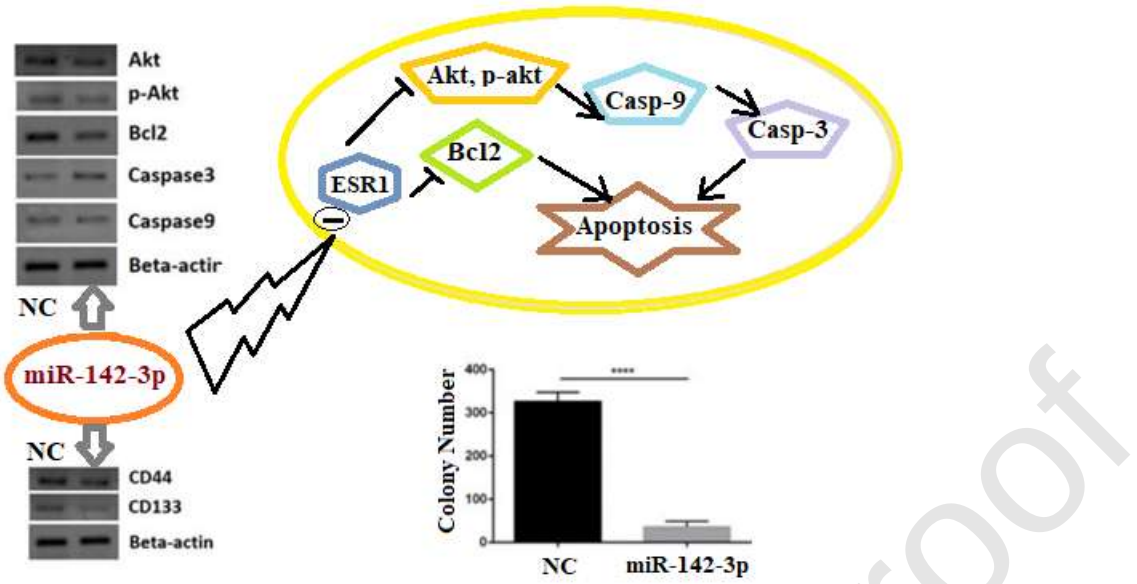

Figure 2. (A) Schematic molecular pathway of miR-142 function in breast cancer cells. (B) Western blot study of the relative protein levels AKT, p-AKT, Bcl2, caspase 3, and caspase 9. (C) Western blot study of CD44 and CD133 bonds following a miR-142-3p transfection in MCF-7 cells. (D) Colony numbers quantified in miR-142-3p- and miRNA-transfected scramble cells [30].

Table1. Effect of miRNA-142 on target genes and their functions in colon cancer. IRAK1(Interleukin-1 receptor-activated kinases 1), CRC (colorectal cancer), Lgr5 (leucine-rich-repeat-containing G-protein-coupled receptor 5), ABCG2 (ATP binding cassette (ABC) G2), RAC1 (Ras-related C3 botulinum toxin substratum 1), CDK4 (Cyclin-dependent kinase 4), Rb (Retinoblastoma), E2F (Elongation factor

2), KLF6 (Kruppel-like factor 6), SDHB (Succinate dehydrogenase-B), EPAS1 (Endothelial PAS domain protein 1).

Table1. Effect of miRNA-142 on target genes and their functions

miRNA-142	Expression in colon cancer	Target gene	Expression of target gene in colon cancer	Function of target gene	Expressing cells	Ref.
miRNA-142-3p	Down-regulation	IRAK1	Down-regulation	Activation of the NF-κB signal caused by LPS in CRC cells, thus decreasing the inflammatory cytokines expression	CRC cells	Zhiying et al., 2013
	Down-regulation	CD133	Down-regulation	raises the proliferation	Colon cancer cells	Shen et al., 2013
	Down-regulation	Lgr5	Down-regulation	raises the coloning formation	Colon cancer cells	Shen et al., 2013
	Down-regulation	ABCG2	Down-regulation	raises the drug resistance	Colon cancer cells	Shen et al., 2013
	Up-regulation	RAC1	Up-regulation	Tumor progression, Tumor angiogenesis and induction of antiapoptotic cell responses	SW480 cells (CRC cells)	Gao et al., 2018
	Down-regulation	CDK4	Down-regulation	CDK4/CDK6 associate with complex of cyclins that can regulate the transition of the G1/S phase cell cycle and prevent Rb binding to E2F	CRC tissues and cells xenografted nude mice	Zhu et al., 2018
miRNA-142-5p	Up-regulation	KLF6	Down-regulation	tumor suppressor in regulating of growth, proliferation, apoptosis and colony formation of cancer cells	SW480 cells (CRC cells)	Islam et al., 2018
	Up-regulation	SDHB	Down-regulation	Control of the energy metabolism	CRC tissues and cell lines	Liu et al., 2017

	Up-regulation	EPAS1	Down-regulation	Selective transcription factor expressed in endothelial cells.	tumor tissues of stage III CRC pateints	Shi et al., 2015