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MicroRNA-221: biogenesis, function and signatures in human cancers

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Abstract. – MicroRNAs are small non-coding RNAs of 18-25 nucleotides that regulate gene expression at the post-transcriptional level through binding to the 3′-UTR of mRNAs and block mRNA transcription or regulate its resistance. Increasing evidence indicates that dysregulation of miRNA is a hallmark of cancer. The miRNAs have an essential role in the regulation of oncogenes or tumor suppressor genes in cell signaling pathways.

MiR-221 and miR-222 are two homologous microRNAs, the high expression levels of which have been commonly demonstrated in multiple human cancer types. The miR-221/miR-222 functions have been verified as oncogenes or tumor suppressors. Here, we reviewed the roles of miR-221/miR-222 in various kinds of cancer progression and development: controlling proliferative signaling pathways, avoiding cell deaths resulted from tumor suppressors, monitoring angiogenesis and even supporting epithelial-mesenchymal transition.

We discussed that miR-221/miR-222 act as promising biomarkers for detection of human cancer types and suggested a new pathway for molecular targeted cancer therapy.

Key Words:
microRNA, miR-221, Oncogene, Tumor suppressor, Angiogenesis.

Introduction

MicroRNAs (miRNAs) are small non-coding RNAs (ncRNAs) of single-stranded RNAs (18-25nt) that control gene expression at the post-transcriptional level via binding to the 3′-UTR of mRNAs and block translation of mRNAs or oppositely regulate their resistance[1,2]. Further miRNA discovery and the increasing research of their common regulatory functions in the cellular processes have presented more insight into regulating gene expression[3]. The aberrant expression of miRNA is leading to the dysregulation of oncogenes or tumor suppressor genes implicated in the cell signaling pathways that causing several diseases, especially cancer. Indeed, through a variety range of mechanisms, the loss and gain of miRNA function involved in cancer cell development. Though miRNAs regulate cancer cell proliferation, differentiation, metastasis and survival, controlling of their expression levels present a perfect remedial procedure towards cancer development[4]. The aberrant expression of miRNAs is detected in several cancer types, instance of breast cancer, prostate cancer, lung cancer, colorectal cancer, lymphoma, leukemia, hepatocellular carcinoma and oral cancer[5-12]. Dysregulation (high or low expression) of these "cancerous" miRNAs confers the tumor development via helping dysregulated proliferation and survival, prolonging invasive behaviors and controlling apoptosis[13,14].

Further reports have illustrated that miRNAs can act as pivotal oncogenes (oncomiRs) or oncosuppressor genes (oncosuppressor-miRs) related to the target genes in the cellular context. MiRNAs can be considerable clues for new tumor markers detection and remedial interpositions in cancer disease as lately represented in other miRNA controlled diseases[4].

This review reveals that miR-221/miR-222 are over-expressed in most epithelial tumors, but can also act as tumor-suppressive miRNAs in erythroleukemic cells through silencing erythropoie-

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sis and the down-regulation of c-kit receptors. In addition, significant reductions of miR-221, miR-222, miR-15a, miR-161, miR-23b and miR-27b expression rates in primary prostate tissues compared with the specimens of marginal non-cancerous prostate tissues were suggested by another study[15,16].

Here, we reviewed a new science on miR-221/222 contributes to cancer cell growth and progression and their pivotal roles as diagnostic, prognostic and remedial tools.

MicroRNA Discovery and Mechanisms

Our recent discovery on miRNAs dates back to gene lin-4 discovery in 1993, which was detected to encode a non-coding hairpin-shaped RNA (22nt) that bounds and blocks the lin-4 mRNA translation in nematodes[17,18]. Seven years later, the regulatory mechanism of this new gene was discovered to have a similar function as let-7 transcription for the post-transcriptional control in nematodes[19]. More similar short non-coding RNAs were detected, through which are determined that these transcripts and their roles were conserved among extensive distant organisms[20,21]. In 2001, 100 short hairpin-shaped RNAs were discovered by several non-related teams using cDNA library sequencing[22-24].

Methodology

Along the elevated miRNAs, a variety of miRNA gene-probes was incorporated using microarray platforms. These widespread methods together with *in situ* detection techniques of miRNAs were applied to a large variety of genomes for determining disease-associated miRNAs[25]. To study the functions of miRNAs and detect their targets, several in-silico algorithms were extended. Homologous mRNA targets to its 5′ seed sequence, moreover, the compensatory binding sites in its 3′ end are usually searched by using these models[26]. The junction of different prediction algorithms has been newly remarked as the most difficult approach to distinguish miRNA targets, create a proper interplay between specificity and sensitivity and decrease the false-positive target prognostics risk[27,28].

Although these in-silico specimens have been substantially applied for miRNA target prognostications, the accuracy of experiential targets yet requires to be verified in terms of miRNA-mediated inhibition at the rate of mRNA and protein levels[29]. Western blots and qRT-PCR associated with luciferase reporter gene technologies are the gold standard. Later, the discovered sequence-related miRNA binding site belongs to the target mRNA incorporating a luminescent reporter was applied. As detected by the decreased luciferase activity technique, a reporter gene participates in the presentation of miRNA binding to the mRNA binding site into a cell line containing the reporter inhibition[30].

A distinction between the high-regulation of a particular miRNA inhibiting of target mRNA translation and its down-regulation destroying the suppression effect is substantial in the miRNA data interpretation. A specific disease outcome is represented by the combined effects of several miRNAs. MiRNA function can only be perceived by understanding its consequences on the cellular mRNA and expression profile of proteins seeking for over-expression or inhibition of miRNA since hundreds of targets may be inhibited by each miRNA, which can affect different downstream molecular pathways. There is no possible explanation for such a function.

The genetically changed mice were used to detect the miRNA effects on mammalians. Homozygous mice lacking of the Dicer-I gene died early during embryogenesis due to their global deficiencies of miRNA synthesis[31,32]. Mice of both sexes (male and female) with the eliminations of partial or conditional Dicer-I genes used for describing the special effects of cells or organs based on postnatal miRNA shortages productively survived into adulthood[33-35].

Based on an indexed miRBase sequence database, 35828 mature miRNA products have been lately identified in more than 223 species[36]. Cloning of nearly 1000 miRNAs has been done in the human genome to target ~30% of the protein-encoding genes that can regulate the transcripts 8000 genes[37-39]. However, just a fraction of these human miRNAs has been recently determined due to the deficiency of extensive empirical methods for verification of miRNA targets. In this research, we achieved to only explain the effects of miRNAs on various cancers.

Biogenesis of miR-221/222 and contribution roles of these microRNAs in mRNA-silencing

In human DNA, chromosome Xp11.3 is the miR-221/222 gene cluster site, which is transported as far as 726bp. The nucleotide sequences of the genes are homologously divided into each other. Indeed, genes are paraloguesly originated from the replication of their ancestral genes.

The promoter region of miR-221/222 genes is contained of 2 canonical TATA boxes placed on 550 and 190 base pairs (bp) upstream of pre-miR-222 and 3 poly (A) signals placed downstream of pre-miR-221. MiR-221/222 gene cluster expression is controlled via Angiotensin II, while it is down-regulated by a repressive complex generated by estrogen receptor α together with the 2 nuclear receptor co-repressors NCOR1 and NCOR2[40,41].

MiRNAs are small non-coding single-stranded RNAs (~24nt) capable of blocking mRNA translation and negatively controlling protein expression via binding to a complementary sequence in the 3′-untranslated region (3′-UTR) of messenger RNAs (mRNAs) as the target genes. The mechanism of miR-221/222 formation in the nucleus usually incorporates a long precursor (pri-miR-221/222) transcription to be then processed to generate the other 110-nucleotide precursor (pre-miR-221/222) via a more specific region of Dorsha/DiGeorge gene 8 as a nuclear protein. The other processing stage is taken via an endoribonuclease of the RNase III family following pre-miRNAs transportation into the cytoplasm with the help of the nuclear transporter exportin-5 as a Ran-GTP protein binding to RNA[42]. To mature miRNA duplexes, miRNA precursors are cleaved by the Dicer. Each miRNA duplex is stabilized by the heterotrimeric complex of Argonaute-2 (Ago-2)/TAR RNA-Binding Protein (TRBP)/ protein kinase R-activating protein (PACT) as an RNA-Induced Silencing Complex (RISC). Double-stranded miRNA is usually an imperfect duplex of transient molecules that include a mature miRNA strand and a passenger strand without a stem-loop structure[43,44]. As the RISC complex (miRISC) joins a functional single-stranded mature miRNA, the duplex is cleaved by Dicer. Some other proteins, including Metadherin (MTDH), glycine-tryptophan protein of 182 KDa (GW182) and staphylococcal nuclease domain-containing protein 1 (SND1) play a remarkable role in miRISC complex generation. The translational inhibition is triggered by the 2 inhibitor domains of GW182 which can affect mRNA destruction. Several repetitions are needed for the generation and protection of the multi-protein RISC-containing complex stability by glycine/tryptophan[45]. As a coactivator of eukaryotic transcription factors, SND1 is a part of ribonucleoprotein complexes containing RISC and spliceosome that promote their functional implementations and dynamics. RNA-binding properties are processed by MTDH in the RISC complex operating as a scaffold protein. Based on a thermodynamic inconstancy, only one strand is incorporated within the selected miRISC[46-48]. There is a formatting possibility of miR-222-3p and miR-222-5p as two mature 21nt-long miRNAs for miR-222 (Figure 1).

The processing of P-bodies has been well explained by the post-transcriptional regulatory functions of miRNAs. RNA destruction and turnover are triggered by the RNA-containing foci that determine P-bodies in the cytoplasm. Although the duplex of miRNA-containing RISC complex was discovered in the cytoplasm, P-bodies were identified to act as the functional location of gene silencing mediated by miRNA[49,50]. Via Watson-Crick base pairing between the guide strand and the 3′-untranslated region (UTR) of the target, binding of the target mRNA to the miRISC complex occurs. The base pairing between the seeds (2-8nt) of the miRNA guide at the 5′ end extremely determines the target distinction accuracy[51,52]. The mRNA target is destroyed by an intense base pairing between the miRNA guide and mRNA target via Ago2-mediated cleavage and deadenylation linked to the complex activity of Ccr4 (mRNA deadenylase), Pop2 (pyrin domain-containing 2) and Not1 (CCR-NOT transcription complex subunit 1). Then, the deadenylated mRNA is decapped by mRNA-decapping (Dcp) and destroyed by exoribonuclease Xrn1p enzymes[53,54]. To inhibit mRNA translation, miRISC complex targets polyribosomes, which translate mRNA in the cytoplasm. The destruction or storage of these mRNAs may lead to translation of transcripts, which is rate-limiting for the cell growth-promoting and they are thus transported to the P-bodies. The regulatory functions of miRNAs are prominent in the cell proliferation, differentiation, progression and apoptotic pathways as various miRNAs of the same or different sequences can even regulate a variety of different transcripts bearing the binding sites. Therefore, the pathogenesis of several human cancer diseases is linked to miRNAs deregulation[55,56].

Angiogenesis, Proliferation and Cell Migration of microRNA-221

High expressions of miR-221 and miR-222 were detected to be derived from c-34-Hematopoietic Progenitor Cells (HPCs) and Human Umbilical Vein Endothelial Cells (HUVECs) in human cord blood. Capillary-like tubes can be shaped in a suitable stimulation by using HUVECs in an *in vitro* model of angiogenesis[57-60]. In a common pri-miR-

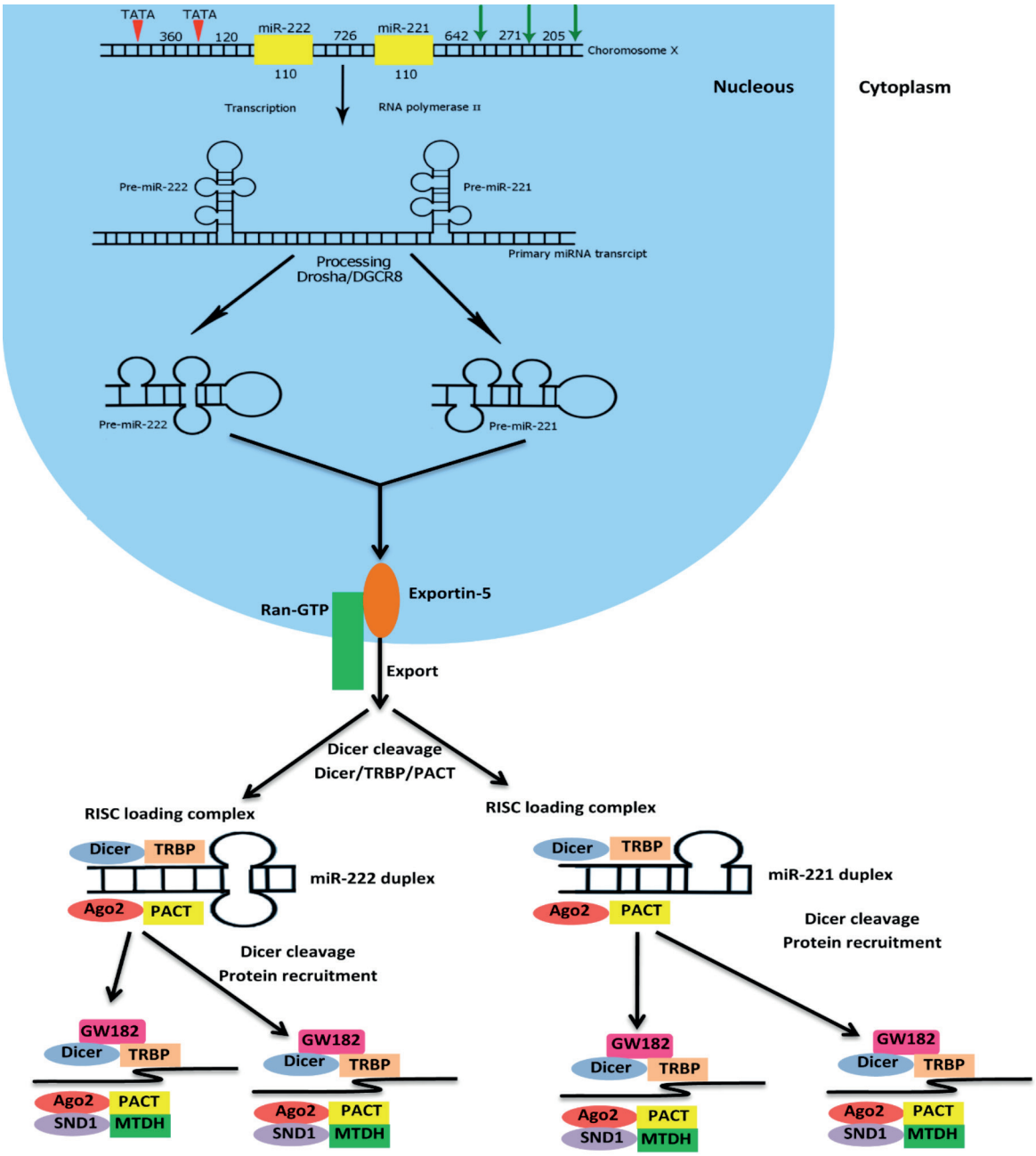

Figure 1. Biogenesis of human miR-221/222. MiRNA-encoding genes are demonstrated in yellow boxes. In the current promoter, TATA boxes are signed by red triangles. Poly(A) signals are showed with green arrows. Numbers determine the interval among the regulatory transcription elements (in bp) and the length of each miRNA gene and intergenic spacer. **DGCR8:** DiGeorge syndrome critical region gene 8; **Ago2:** Argonaute-2; **MTDH:** metadherin; **GW182:** glycine-tryptophan protein of 182 kDa; **TRBP:** TAR RNA-binding protein; **SND1:** staphylococcal nuclease domain-containing protein 1; **PACT:** protein kinase R-activating protein; **Ran-GTP:** GTP-binding nuclear protein Ran.

NA, a coordinated transcriptional control of gene regulation can be confirmed via miR-221/222 in c-kit-positive HUVECs. The post-transcriptional down-regulation of these miRNAs on the c-kit protein was detected by more and more groups looking for the effects of miR-221/222 expression on the c-kit transcripts and proteins. They found a decline in HUVECs transfected with miR-221/222 that was caused by the c-kit protein level without a change in expression levels of mRNA. However, no wound-healing or tube shapes were suitably resulted from miR-221/222 transfected cells[59].

Other studies investigated that miR-221/222 can down-regulate endothelial Nitric Oxide Synthase (eNOS) as an important regulator of angiogenesis though the regulation was detected to be indirect in terms of gene expression, transcriptional efficiency and post-transcriptional pathways because of the non-existence of any target sites for these microRNAs in the 3′-UTR of eNOS[61]. It is noteworthy to say that cell growth proliferation and angiogenesis were decreased via miR-221/222 up-regulation in the endothelial cells, while cell proliferation was inversely enhanced by miR-221/222 high-expression in cancer specimens via targeting the cell-cycle inhibitor P27[62].

Glioblastoma and microRNA-221

Glioblastoma causes the most recurrent brain tumor of human cancers among adults. Contrary to the improvements combination of therapies including surgery, radiotherapy and chemotherapy, there is still a low survival rate[63]. Several studies[64-67] have revealed that the diverse oncogenes of miRNAs and tumor suppressor genes are involved in the formation, growth, migration and invasion of glioma. Several researches have reported that miR-221/222 in glioma tissue specimens and glioma cells may directly control apoptosis through targeting the molecular high-expression of P53 enduring apoptosis[68]. Up-regulation of miR-221/222 can suppress PTPμ protein-tyrosine phosphatase expression that inversely controls cell migration, thus increasing tumorigenesis of glioma cells[69]. Recent evidence[70] showed that miR-221/222 can develop angiogenesis and metastasis of glioma cells via targeting TIMP2 as the tissue inhibitors of metalloproteinases, therefore suppressing the activity of MMPs (matrix metalloproteinases) as a result conserving the Extra-Cellular Matrix (ECM) from proteolytic destruction and causing low-expression of the reproduction of endothelial cells.

Bladder Cancer and microRNA-221

One of the universally diagnosed malignancies among genitourinary tumors is bladder cancer (BC)[71]. Thus, it is helpful to comprehend the molecular and cellular process of metastasis in search of bladder cancer development. In other available studies, it was illustrated that miR-221 expression is highly expressed in TGFß1-responsive bladder cancer cells and plays a considerable role in EMT phenotype progression. EMT is determined via a modified morphology, lack of intercellular junctions, promoted motility, confined proliferation and changes in gene expression. The above work indicated that miR-221 can support the TGFß1-induced EMT procedure in human bladder cancer cells via inhibiting the expression of STMN1. Therefore, targeting STMN1 and miR-221 regulation mechanisms via TGFß1 induction provides promising practical choices for the remedy and suppression of human bladder cancer cells[72]. Also, another investigation detected that high expression of miR-221 associated with down-regulation of SOCS3 in bladder tumor tissue. Suppression of miR-221 inhibited T24 cell proliferation and triggered apoptosis through the high-expressing SOCS3 level, reducing JAK-STAT3 signaling pathway activity and weakening surviving expression[73].

Prostate Cancer and microRNA-221

Prostate cancer is a complex and multifactorial disease among men which is associated with environmental factors and genetic variations. In prostate tissue specimens and cells, scholars have detected that miR-221, miR-222, miR-30a and miR-30d can bind with the 3′-UTR of Bmi-1. The miR-221 expression has been discovered to significantly decrease in prostate cancer tissue samples compared with the increased Bmi-1 expression. MiR-221 and miR-30d can be considered as oncosuppressor-miRs in prostate cancer[74]. The aberrant expression of miR-221/222 and miR-203 can change responses in prostate cells to androgen remedy, thus offering their potential involvements in the transferring to human Castration-Resistant Prostate Cancer (CRPC). Moreover, the expressions of miR-23b, -27b, -15a and -16-1 did not have noticeable effects on the responses of cells to androgen remedy, thus indicating that these microRNAs may not act as a remarkable role in the CRPC phenotype. The analyzed metastatic CRPC tumors could show promoted miR-221/222 and down-regulated miR-23b/-27b expressions[16].

The raised expression of miR-221/222 related to CRPC and miR-221/222 targets, HECTD2 and RAB1A pivotally interferes to the promotion of the CRPC phenotype. The decreased expression of HECTD2 has a considerable role in changing the Androgen Receptor (AR) signaling pathways. The low expressions of HECTD2 and RAB1A result in an androgen-independent cell development and growth. Moreover, the high expression of miR-221/222 down-regulates HECTD2 and RAB1A that then result in the reprogramming of AR pathways and can trigger new cyclin activation, which leads to the CRPC phenotype

promotion. Exclusively, the growth of cdc20, an AR-controlled G2-M-phase cell cycle regulator, is induced by HECTD2 down-regulation, which probably leads to androgen-independent cell promotion[75].

Pancreatic Cancer and microRNA-221

To find out a significant effect of microRNA roles in pancreatic cancers, the expressions of over 200 microRNA precursors were surveyed in benign tissues, normal pancreas specimens, chronic pancreatitis specimens and pancreatic cancer cell lines using Real-time PCR technology. The results were indicative of mature up-regulation of miR-221/222 in pancreas cancer[76]. Recent researches have demonstrated miR-221/222 expression in primary human pancreatic tissues and their other oncogenic roles in pancreatic cancer cells. Therefore, the expression of miR-221/222 was up-regulated in human pancreatic cancer that inhibited apoptosis and enhanced proliferation and invasion of pancreatic cancer cells. The increased rate of expression in MMP-2 and MMP-9 after mimic transfection demonstrated that TIMP-2 is a direct functional target of miR-221/222. MiR-221/222 enhanced cell proliferation and growth by reducing G1-phase and apoptotic cells. Furthermore, miR-221/222 straightly bound TIMP-2, up-regulated MMP-2 and MMP-9 expressions, and enhanced cell invasion[77]. Another study revealed that miR-221 plays as an oncosuppressor-miR in pancreatic cancer tissues[15,78-80]. Also, miR-375 was reported to have a tumor suppressive role in pancreatic cancer[80]. Accordingly, plasma miR-221 concentrations may act as sensible clinical intentions to pancreatic cancer remedies[81].

Colorectal Cancer and microRNA-221

Colon cancer occurs in the digestive tract, i.e., at the junction of the rectum and sigmoid colon[82]. In a recent study[83], it was detected that the expression levels of miR-221-3p, miR-342-3p and miR-491-5p influenced the detection of early colon cancer patients. Dysregulation of miR-221 indicates the growth and prognosis of CRC. MiR-221 confirmed an oncogenic characteristic in CRC. High miR-221 expression enhanced CRC cell invasion and metastasis through targeting CDKN1C and RECK[84-86]. Besides, the miR-221-3p is up-regulated in colon cancer and is a pivotal prognostic biomarker for detecting this cancer. Nevertheless, opposed to the upper-sign outcomes, Yuan et al[87] discovered that the passenger strand of miR-221 is low-expressed in CRC and displays tumor suppressor-like properties. Also, it was reported that the enhanced expressions of miR-200c, miR-221 and miR-222 and diminished expressions of let-7b and PTEN proteins are controlled by oncogenic KRAS using a 3D-specific method. The elevated expressions of 3D-specific miRNAs containing miR-200c, miR-221 and miR-222 were as well as discovered in these tumor specimens. The high expression of miR-221 had the low survival rates. So miR-221 could serve as a molecular marker for the prognosis of colon cancer[88,89].

Gastric Cancer and microRNA-221

Gastric Cancer (GC) is the most recurrent leading cause of gastrointestinal cancer-related deaths between adults[90]. Former researches have displayed serum tumor markers diversity, for instance, carcinoembryonic antigen and carbohydrate antigen 19-9 to support the early discovery of gastric cancer. Yet, tumor markers are not reasonably specific for the early discovery of cancer. RNA markers containing mRNA and miRNA have been proved in gastrointestinal cancers[91-94]. Moreover, miR-221 was up-regulated in about 88% of gastric cancer tissue specimens comparing with their marginal non-cancerous tissues[95]. In a current study[96], it was discussed that miR-221 and miR-222 are high-expressed after *H. pylori* infection disease. High serum levels of miR-221/222 are relevant to clinical stages and metastasis of lymph nodes in gastric cancer. Up-regulated miR-221/222 considerably suppress the RECK expression, thus promoting cell proliferation and growth in gastric cancer[97]. It was discussed that several miRNAs can suppress RECK expression and thus elevate gastric cancer progression via miR-21, miR-25, miR-222 and miR-374[98-101]. Moreover, in a recent study[102], it has been realized that miR-221 and miR-222 can use PTEN as a target gene, thus they can regulate cell proliferation and radio-resistance in gastric carcinoma. In addition, it was confirmed that miR-21 and miR-221 over-expressed in gastric tumor tissues. Thus, both of them can be potentially applied as novel biomarkers for the primary discovery of gastric cancer at early stages[103].

Thyroid Cancer and microRNA-221

Follicular Thyroid Carcinoma (FTC) and Papillary Thyroid Carcinoma (PTC) are the significant histological categories of thyroid carcinoma worldwide[104-106]. An aberrant microRNA expression profile that noticeably differentiates PTCs from normal thyroid tissues has been lately dis-

covered through the analysis of the genome-wide miR expression profile in human PTCs and miRNA CHIP microarray application. The high miR-221, miR-222, and miR-181b expressions have been analyzed in PTCs. This report suggested a novel mechanism of P27Kip1 protein regulation related to the miR-221 and miR-222 over-expressions as characterized in PTCs. MiR-221 and miR-222 were shown to significantly control P27Kip1 mRNA translation since conversely controlling of P27Kip1 gene expression that produced at the 3′-UTR-based reporter. This controlling of regulation is related to the 2 target sites placed at the 3′-UTR of P27Kip1 gene[107]. Essential data on the molecular diagnostic and new remedial ways for MI-FTC has been provided by another study on FFPE specimens through Laser Micro-Dissection (LMD) application. In addition, the expressions of miRNAs relevant to the miR-221/222 cluster, miR-10b and miR-92a were discovered to be considerably up-regulated in the metastatic MI-FTC. Thus, miR-10b displayed to be a pivotal prognostic biomarker for MI-FTC at a primary operational stage[108].

Breast Cancer and microRNA-221

The most prevalent of cancer deaths among women is Breast Cancer (BC)[90]. More than one million women have been annually suffering from BC worldwide. BC can invade local tissues aggressively and trigger early metastasis, thus showing low-chemosensitivity[109,110]. In spite of the advances of modern treatment based on the chemotherapy and radiotherapy, a low rate of long-term survival has remained in patients with progressive BCs[111]. Hence, BC remedy is linked to the detection of the mechanisms underlying BC and extension of the sensitivities of cancer cells to chemotherapy. As shown by the evidence, miR-221 knockdown considerably reinforces the curative consequence of cis-dichlorodiammineplatinium (II) (DDP) as one of the first-line chemotherapeutic agents highly utilized as a remedy of variety of human cancers containing breast cancer cell lines though cell viability is not directly suppressed by anti-miR-221[112]. Also, BIM (a BH3-only protein as a pro-apoptotic member of Bcl-2 family located in the mitochondrial membrane) as a clue regulator of apoptosis was found out to be a target of miR-221, while its level of expression was considerably high-expressed through miR-221 knockdown[112,113].

Another study[114] has lately shown that slug transcription and miR-221, which are relevant to an aggressive phenotype, are expressed in breast cancer cell specimens containing MDA-MB-231 cell line. The detection showed that miR-221 is a part of the slug transcription in breast cancer cells and that slug transcription factor acts as essential role in miR-221 function during the cancer cells to undergo migration and invasion. Also, the ERα expression through the post-transcriptional level is suppressed via miR-221/222 high-expression, which causes an estrogen-independent growth. Moreover, the expressions of varied tumor suppressors like BIM, PTEN, TIMP3, FOX03, CDKN1B, CDKN1C and DNA damage-inducible transcript 4 are suppressed by this miRNA over-expression, which leads to a high proliferation[40].

Hepatocellular Carcinoma and microRNA-221

The primary liver cancers contain hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC) and hepatic angiosarcoma[115]. HCC is the fifth most prevalent malignancy between human cancer patients and the third most current reason of cancer-relevant mortalities[116]. HCC elevation occurs during the multistage process of deregulation of the genes contribute to the cell-cycle control, cell migration and apoptosis. MicroRNAs (miRNAs) are included in the molecules that regulate these events[117]. The researchers of the present study demonstrated a remedy for the tumor-bearing mice with chol-anti-miR-221, which resulted in a survival superiority compared with the mice performed to cholesterol-modified control oligonucleotides. These detections supported an anti-tumoral outcome of targeting miR-221 as the most substantially expressed miRNA in HCC. Also, it was discovered how the tumoral expressions of P27kip1, P57kip2 and PTEN are triggered via chol-anti-miR-221. Thus, changes in these factors help to limit the tumor cell-cycle promotion in a mechanism, by which chol-anti-miR-221 elevates the survival rate of tumor-bearing mice[118]. Related to another report miR-221, which is up-regulated in large cases of HCC, has an oncogenic role in suppression of CDKN1C/P57 and CDKN1B/P27 protein expressions. These outcomes made a real effect for the promotion of remarkable remedial procedures considered as blocking miR-221 expression in HCC[119].

Leukemia and microRNA-221

Chronic Lymphocytic Leukemia (CLL) is distinguished as the most current leukemia via the accumulation of malignant mature monoclonal

$CD5^+$ B lymphocytes in the Peripheral Blood (PB), Bone Marrow (BM) and lymphoid organs[120]. In a latest paper[121], it was discussed that miR-221/222 regulates the expressions of P27 in CLL cells as in any other kinds of cancers. This regulation might induce leukemic cells to enter the cell cycle following the microenvironmental interactions and stimulation by the tissues and sustain CLL lymphocytes in the bloodstream under resting conditions. The miR-221/222-P27 system may then display a modulatory loop that is involved in the survival/proliferation sensitivity in CLL. In another study[122], it was reported that miR-128b and miR-221, particularly miR-128b, are functionally significant in lymphoid cell biology. Most noticeably, the effects of miR-128b and miR-221 on drug resistances are cooperative, while the combination of these miRNAs aims at a hopeful target for the disease therapy.

Lung Cancer and microRNA-221

Beginning of cancer in the lung are recognized as primary lung cancer carcinomas. The two remarkable kinds of lung cancer are Small-Cell Lung Carcinoma (SCLC) and Non-Small-Cell Lung Carcinoma (NSCLC)[123-125]. Molecular epidemiologic researches demonstrated that there are hundreds of genes having a role in lung carcinogenesis. The researchers of the current investigation showed the inhibitive effects of miR-221 and miR-222 in lung cancer cells. Suppression of the growth and development of lung cancer via miR-221 or miR-222 happened through S-phase cell cycle arrest and apoptosis partly resulted from DNA Double-Strand Breaks (DSBs). Their outcomes represented that miR-221 or miR-222 can cause promotion of S-phase targeting drugs sensitivities, including cisplatin and gemcitabine, but do not affect the M-phase targeting drugs, such as paclitaxel[126,127]. However, opposite with this research, Garofalo et al[128,129] discussed that miR-221 and miR-222 as two oncosuppressor-miRs elevated the tumorigenic phenotypes of H460 lung cancer cells associated with invasiveness and resistance to TRAIL-induced apoptosis via suppressing PTEN and TIMP3. MiR-221 and miR-130a control regulation of airway branching and lung microvascular progression by targeting the developing vasculature. It was comprehended that the promoted miR-221 or diminished miR-130a levels in lung cultures produce a disarranged vascular network related to the limited airway branching[130]. The branched airway was dilated to observe a phenotype associated with over-expression of the VEGFR1 decoy receptor in the lung that is knocked down in the FIK-1 receptor. Anyhow, this was the novel study to display that miRNAs contributed to the critical processes of coordinated airway and blood vessel progression[131,132].

Cervical Cancer and microRNA-221

Cervical cancer is the most prevalent cancer that often affects women and is the leading cause of malignancy-related death among female[133]. The cancer is caused by multiple kinds of a virus called human papillomaviruses (HPV)[134,135]. Up-regulation of miR-221 and miR-222 after HPV infection was detected in former researches[136,137]. The current study showed that miR-222 plays a significant role in the carcinogenesis of CC, presumably through particularly down-regulating p27Kip1 and PTEN[138]. Also, high expression of miR-221 in cervical cancer cells reduced PTEN expression level, which associated with the promotion of pAkt and BCL-2 expressions. Consequently, it was reduced by the high expression of miR-221, which was blocked by pcDNA-PTEN co-transfection or by the phosphatidylinositol-3 kinase (PI3K) inhibitor LY294002[139]. Another work[140] illustrated that high expression of miR-221 and miR-222 associated with the ARID1A loss in cervical cancer. The miR-221/222-ARID1A axis can regulate proliferation and invasion of cervical cancer cells.

Conclusions

The above investigations supported the viewpoint that the detection of the pivotal roles of miRNAs in cancer has illustrated a new era in front of cancer scholars to evaluate new science about RNA signaling systems. From among several miRNAs detected as the modulator of neoplastic transformation, invasion and metastasis, as the key miRNAs deregulation of miR-221/222 have discovered in many human cancer types. However, comprehending of their signaling pathways has lately achieved its primary stages even though miR-221/222 has been realized as the most drastic miRNAs studied so far. The solutions to suchlike RNA signaling pathways will provide a comprehending act of the deregulated miRNAs in oncogenic procedures, through which new remedial molecules may be significantly defined. Such remedies may contain silencing oncomiRs or gene therapy procedures depended on the re-expressions of low-expressed miRNAs in cancer cells. Nevertheless, various detections

are necessary to extend these discoveries from *in vitro* to prosperous *in vivo* transferring systems, which depend on limb especially with less or no toxicity and without off-target outcomes.

In this review, we discussed that dysregulation of miRNA-221 is commonly observed in cancers. Overexpression of miRNA-221 inhibits tumor suppressors and genes involved in apoptosis, cell cycle inhibition and miRNA processing, and promotes tumor cell growth and development in a number of advanced malignancies. Therefore, whether on one side miRNA-221 is detected high-expressed in the majorly invasive tumor, on the other side patients with higher miRNA-221 levels could respond better to the remedy.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

MiRNA and cell type	MiRNA targets (direct or indirect)	Function (by MiRNA overexpression or inhibition)	References
MiR-221 ER-α-negative breast cancer cells, MDA-MB-231 and MDA-MB-436	Slug (SNAI2) transcription factor, ER-α, TRPS1, E-cadherin	The most contribution to the invasion ability of the cells and their aggressive phenotype (EMT) comes from slug rather than miR-221.	114
MiR-221/222 ER-α-positive breast cancer cells, T470, MCF7, MDA-MB-231, and MDA-MB-436	FOXO3, CDKN1B, BIM, CDKN1C, PTEN, TIMP3, DDIT4, ERα, ERBB2	The promoted of miR-221/222 may confer a proliferation benefit to cancer cells and further resistance to remedial factors by inhibiting the expression of ERα, CDKN1B, CDKN1C, BIM- FOXO3-CAV1-CAV2-PTEN and progesterone receptor.	40, 119, 129, 141, 142
MiR-221/222 Brest cancer cell lines (MCF7, MCF-7-F, and BT474 cells)	CTNNB1 (ß-catenin), FZD5, Wnt5A, TGFBRR2, BMPR2, SMAD2, ID1, ID3, P53, P21, Cip1, PERP, CASP3, FAS, IGFBP3, GADD45A, SESNs (SESTRINs), CAV1, CAV2, P27, CCL5, GDF15, CXCR4, STAT1	Ectopic expression of miR-221/222 enhances ER-independent growth and confers resistance to fulvestrant.	143
MiR-221/222 Glioma cell lines U87, U251, SHG-44, BT325, and A172	TIMP2	MiR-221/222 promotes angiogenesis and metastasis of glioma cells by suppressing TIMP2.	70
MiR-221/222 and miR-200c Human colorectal cancer HCT116 cells and Hke3 cells	KRAS, let-7b, PTEN	The enhanced expression of miR-200c, miR-221, and miR-222 and diminished expression of let-7b and PTEN protein are regulated by oncogenic KRAS in human colorectal tumor specimens.	88
MiR-221 Human bladder cancer cell lines (RT4 and T24)	Stathmin1/oncoprotein 18(STMN1)	MiR-221 can facilitate the TGFß1-induced EMT process in human bladder cancer cells by inhibiting STMN1.	72
MiR-221-3p, miR-342-3p, miR-491-5p, miR-203-3p, and miR-503-5p Colon cancer specimens	_	High expression of miR-221-3p, miR-342-3p, and miR-491-5p elevated colon cancer cell invasion and metastasis.	83
MiR-221 Breast cancer cell lines (MDA-MB-231, BT-20, MDA-MB-435, andT-47D), non-malignant breast epithelial cell (MCF-10A), and breast cancer tissue specimens	BIM, Bak/Bax	In breast cancer, up-regulation of miR-221 induced the invasive phenotype of tumor cells, whilst knockdown of it converted this phenotype via up-regulation the expression of BIM, Bak/Bax.	112
MiR-221/222, -30d, and -15a Prostate cancer cell lines (PC-3 cells and HEK293T) and prostate cancer patient's tissues	Bim-1	The expression of miR-221 and miR-30d was considerably diminished in the prostate cancer tissues accompanied with elevated Bmi-1 expression. The miR-221, and miR-30d species are candidate as tumor suppressor miRNAs in prostate cancer.	74

Table continued

MiR-221, -222, -23b, -27b, -15a, -16-1, and -203 Prostate cancer hormone sensitive LNCaP cell line and the hormone resistant LNCaP-abl cell line and prostate cancer patient's tissues	_	Up-regulation of miR-221/-222 and down-regulation of miR-23b/-27b were detected in association with the human prostate cancer progressing to CRPC (castration resistance prostate cancer).	16
MiR-221 Triple negative breast cancer cell lines (MDA-MB-231, Hs578T, BT20, MDA-MB-468, SKBR3, MDA-MB-361, T47D, ZR75-1 and MCF-7)	P27kip1, E-cadherin, Snail, Slug	MiR-221 is a potential oncomiR and functions as an oncogen to enhanced cell cycle progression of TNBCs by inhibiting P27kip1 and suppressing the expression of E-cadherin to mediate EMT transition.	144
MiR-221/222 ER-positive breast cancer cell lines MCF-7^{Wt} (tamoxifen sensitive) and MCF-7^{TamR} (tamoxifen resistance)	_	Exosomal miR-221/-222 can elevate tamoxifen resistance by signaling to the recipient ER-positive breast cancer cells.	145
MiR-221 Breast cancer cell line MDA-MB-231 and mouse fibroblast cell line NIH3T3	PTEN	MiR-221 contributed to TRAIL-resistance through targeting PTEN that can improve migration and invasion and induced EMT.	146
MiR-221/222 Breast cancer cell line MDA-MB-231, MCF7, MCF10A and CAL-85-1	TRPS1	MiR-221 affluence is positively regulated by the EGFR, RAS, RAF, MEK, ERK2, FOSL1 axis and promotes EMT by targeting TRPS1, which straightly suppresses the transcriptional of ZEB2. As a result of promoted miR-221/222 affluence, ZEB2 abundance elevates, permitting the inhibition of E-cadherin and high-regulation of vimentin to elevate EMT.	147
MiR-221/222 Breast cancer cell line MDA-MB-231, MCF7, MDA-MB-453 T-47D, Hs578t and SUM159 cells	SOCS1 and CDKN1B	High expression of miR-221/222 in basal-like subtype of human breast cancer promotes breast cancer cellular migration, invasion, and s-phase entry of cell cycle. Two tumor suppressor genes, suppressor of cytokine signaling 1 (SOCS1) and cyclin-dependent kinase inhibit 1B (CDKN1B), are conversely regulated in expression by both miR-221 and miR-222.	148
MiR-221/222 The human breast carcinoma cell lines MCF7, MDA-MB-361, and T47D The rat bladder epithelial cell line 804G The human mammary cell line MCF10A	ß4-integrin and STAT5A	MiR-221/222 high expression outcome in ß4-integrin expression down regulation, breast cancer cell proliferation, and invasion suppression. These two miRNAs also play crucial role in breast cancer cell proliferation and invasion regulators, through the post-transcriptional regulation of signal transducer and activator of transcription 5A (STAT5A) and of a disintegrin and metalloproteinase-17 (ADAM-17).	149
MiR-221 Breast cancer cell line T47D	DNMT3b, Nanog, CK18, CK8, E-cadherin, Slug, Zeb1, Oct3/4, ß-actin, Sox2	MiR-221 induces expression of pluripotency-associated genes, including Nanog, Oct3/4, and ß-catenin, enforcing stemness and mammosphere formation. MiR-221 down regulation DNMT3b expression, modifying BCSC phenotype.	150
MiR-221 SNU-398, HepG2, and HEK293 cell lines	E2F, MYC, NF-κB, FASLG, RB1, WEE1, APAF1, ANXA1, CTCF, ß-actin	MiR-221 induced a reduction in RB1, CTCF, APAF1, ANXA1, and WEE1 proteins in SNU398 cells. In addition four pathways, MYC, MAX, NF-κB, Wnt/ß-catenin, and RB-E2F, were considerably elevated by miR-221 over expression.	151

Table continued

MiR-221 Prostate cancer cell lines LNCaP and LNCaP-Abl cells, LAPC-4 cell line, and PC-3, Du145 and 22Rv1 cell lines	HECTD2, RAB1A, JAG1, NOTCH1, NOTCH2, WNT5A, GSK3B, CTNNB1, EZH2, HRAS, KRAS, CDH3, CDH1, ADRB2, ERBB2, MAPK1	1) Up regulation of miR-221/-222 down regulated HECTD2 and RAB1A, that subsequently regulated in reprogramming of AR pathways and activation of new cycles, causing the progression of the CRPC phenotype 2) Up regulation of miR-221/-222 actives several important EMTor tumor metastasis regulators, containing GSK3B, EZH2, WNT5A and RAS, JAGG1/Notch1/Notch2 were up regulated both in LNCaP-Abl and LNCaP, but expression of cadherin (CDH1 or CDH3), ERBB2, MAPK1 and ADRB2 were down regulated in LNCaP-Abl and LNCaP.	75
MiR-221 Prostate cancer tissue specimens	TMPRSS2, ERG	Down regulation of miR-221 is related with the presence of the oncogenic TMPRSS2: ERG fusion transcript that leads to more aggressive tumors.	152
MiR-221 Prostate cancer cell lines DU145, PC-3, and LNCaP cells and Prostate cancer tissue specimens	IRF2, SOCS3	MiR-221 has tumor suppressive role in prostate cancer controlling cell growth, apoptotic pathways and invasiveness. The antitumorigenic effect of miR-221 expression is mediated at least partially by activation of the JAK/STAT pathway. MiR-221 regulates two of the most important negative regulator proteins, SOCS3 and IRF2, of the JAK/STAT signaling pathway.	153
MiR-221/222 Gastric cancer tissue specimens and gastric cancer cell lines HEK293T, AGS, GES-1, BGC-823 and SGC-7901	RECK	MiR-221/222 were up-regulated after *H. pylori* infection. Elevated MiR-221/222 considerably suppresses RECK expression, so promoted gastric cancer cell proliferation.	96
MiR-221 Pancreatic cancer tissue samples and pancreatic cancer cell lines PK-45H, PANC-1, PK-59 KP4-1, PK-1, and NOR-P1 and plasma of patients with pancreatic cancer	–	1) Concentration of oncogenic miR-221 was promoted in plasma of patients with PCs, and concentration of tumor suppressive miR-375 was diminished in plasma of patients with PCs 2) Expression levels of miR-221 in PCa tissues and PCa cell lines were significantly higher than those in normal pancreatic tissues.	81
MiR-221/222 Pancreatic cancer tissue samples and pancreatic cancer cell lines Panc-1, Miapaca2, Bxpc2, and SW-1990 and the human embryonic kidney cell line HEK293	MMP-2, MMP-9, TIMP-2	High expressed miR-221/222 could suppress TIMP-2 and consequence up regulation the expression of MMP-2 and MMP-9, which could elevate the invasion of pancreatic cancer cells.	77
MiR-221 Human bladder cancer cell lines T24, 5637, and J82	PUMA, VEGF-C, MMP-2, MMP-9	High expression of miR-221 in bladder cancer cells suppresses the expression of the pro-apoptotic gene PUMA, therefore suppressing the transduction of apoptotic signals. Also, the down regulation of miR-221 in bladder cancer cells reduced the expression of VEGF-C, MMP-2 and MMP-9, outcoming in reduced invasion of bladder cancer cells.	154

Table continued

MiR-221/222 The human breast cancer cell line MCF-7	PTEN/Akt pathway	Over expression of miR-221/222 cluster down regulated the expression of the PTEN in breast cancer cells and the downstream Akt pathway is activated. MiR-221/222 enhanced breast cancer livability, migration and invasion, and propagation of BCSCs, at least in part, via targeting PTEN/Akt pathway.	155
MiR-221 Breast tumor stem cells BTSCs, T47D cells	DNMT3b	MiR-221 was high regulated in BCSCs compared to marginal counterpart. In addition mammospheres from T47D cells had an elevated level of MiR-221 compared to differentiated cells. MiR-221 induces expression of pluripotency-associated genes, such as Nanog. Oct3/4, and ß-catenin, enforcing stemness and mammosphere formation. MiR-221 down regulates DNMT3b expression, modifying BCSC phenotype.	150
MiR-221 The human breast cancer cell line MCF-7 and MDA-MB-231	Slug, E-cadherin	Slug up regulation miR-221 expression, targets the ORF of E-cadherin mRNA transcript via direct binding to the E-boxes of E-cadherin promoter, and suppresses the protein production of E-cadherin at post-transcriptional level in metastatic tumor cells. Relevant with slug-promoting miR-221 in metastatic tumor cells both slug and miR-221 were up regulated by TGF-ß.	156
MiR-221/222 Breast tumor tissue specimens and breast cancer cell lines the T47D, SK-BR-3, and MDA-MB-361	P27kip1	Over expression of miR-221/222 is considerably associated with the occurrence of distant metastasis in breast cancer. There was an opposite correlation between P27kip1 protein levels following the high expression of miRNAs. Besides there was an reverse association between miR-221 and ER expression in tumor tissues allows for remarkable realizing of different prognostic groups, particularly, in advanced (LN+, HER+) breast cancers.	157
MiR-221/222 Mouse myoblast cell line C2C12 cells	MyoD	1) MiR-221/222 were able to target myoD in C2C12 cells by binding with its 3′-UTR at positions 383-389 and inhibit myo-D gene expression 2) MiR-221/222 were determined to the differentiation, proliferation, maturation, and regeneration of skeletal muscle.	158

Table continued

MiR-221/222 The 22 lung cancer cell lines and one cdk4/hTERT, immortalized normal human bronchial epithelial cell line, HBEC4, and six cell lines including three EGFR-wild-type cell lines (H460, H838, H1299) and three EGFR-mutant cell lines (H3255, HCC4006, HCC4011)	PTEN	1) MiR-221/222 promoted growth in H460, while in other five cell lines miR-221 suppressed growth in four cell lines without modifying one and miR-222 inhibited growth in the three cell lines but elevated growth in two. These results were the first to showed growth suppressive effects of miR-221/222 in lung cancer cells. Growth suppression through miR-221/222 happened via S-phase arrest and apoptosis in part consequencing from DNA DSBs 2) MiR-221/222 elevated sensitivities to the S-phase targeting drugs cisplatin and gemcitabine but did not affect an M-phase targeting drug, paclitaxel 3) MiR-221/222 elevated tumorigenic phenotypes of H460 lung cancer cells through inhibiting PTEN.	127
MiR-221 Breast cancer cell lines SKBR3, MCF7, HCC1500, ZR-75-1, MDA-MB-231, Htert-HME1	PAK1	MiR-221 targeting 3′-UTR region of PAK1 gene that can be suppressed tamoxifen resistance in ER+ breast cancer patients.	159
MiR-221 Human colorectal cancer cell lines SW480, HCT116, HT29, L0V0 and SW620	RECK	MiR-221 expression considerably elevated CRC cell invasion and metastasis *in vitro* and *in vivo* possibly as a result of targeting MMP suppressor RECK by binding to the RECK 3′-UTR.	85
MiR-221 Breast cancer tissue specimens	–	MiR-221 expression was elevated in breast cancer tissues compared with non-cancerous tissues and was relevant with advanced clinical stage of the tumor.	160
MiR-21 and MiR-221 Gastric cancer tissue samples	–	MiR-21 and MiR-221 were considerably high-expressed in gastric cancer tissues compared with non-tumor tissues.	103
MiR-221 Colon cancer tissue samples	–	MiR-221 was considerably over-expressed in colon cancer tissues, thus in colon cancer patients with low expression of miR-221, the survival time was longer; in contrast patients with up regulation of miR-221 had shorter survival.	89
MiR-221/222 The human gastric cancer cell line SGC7901 and the human embryonic kidney cell line HEK293	PTEN	MiR-221/222 affected gastric cancer cell viability, apoptosis, cell cycle progression and invasive ability through suppressing of PTEN expression, therewith elevating Aκt phosphorylation through activated PIP3.	102
MiR-221 Gastric cancer tissue samples	–	High expression of miR-221 was relevant with tumor promotion and poor prognosis in patients with gastric cancer.	95
MiR-221 The human glioma cell lines U87, U251, SWOZ and the BCUN-resistant SWOZ2	PI3-K/PTEN/Aκt signaling axis	MiR-221 regulates cell proliferation and BCNU resistance at least through the PI3-K/PTEN/Aκt signaling axis in human glioma cells.	161
MiR-221/222 The human glioma cell lines U87MG, T98G, LN-308, LN-319, A-172, LN-428, LN-18 and LN-229	PTPμ	MiR-221/222 regulate glioma tumorigenesis through down-regulating of PTPμ protein expression.	69
MiR-221/222 The human glioma cell lines A172, U251, H4, LN299, retrovirus-packaging cells PT67 and the mouse fibroblast cell line NIH3T3	PUMA	MiR-221/222 induced cell survival by targeting PUMA, and so regulates mitochondrial pathway.	162

Table continued

MiR-221 Hepatocellular cell line PLC/PRF/5	–	MiR-221 inhibiting blocks hepatocellular carcinoma and promotes survival.	118
MiR-221 Hepatocellular carcinoma cell lines HepG2 (ATCC HB-8065) and Hep3B (ATCC HB-8064) and the human embryonic kidney cell 293FT	–	The recent "miR-221 sponge" vectors, that can diminish oncogenic miR-221 activity *in vitro* and also for *in vivo* delivery in HCC cell lines.	163
MiR-221 Human HCC cell line HepG2 cells	PTEN, P27kip1, TIMP3	In gene therapy of HCC, oppositely charged liposomal delivery system was utilized for delivering miR-221 antisense oligonucleotide (anti-miR-221) to the transferrin receptor high expressed HepG2 cells, so up-regulated miR-221 target genes PTEN, P27kip1, and TIMP3, and could be a potential remedial in the gene therapy of human HCC.	164
MiR-221 Human HCC cell lines Hep3B-Con, Hep3B-SND1-17, QGY-Consi and QGY-SND1si-12 and the human vascular endothelial cells (HUVEC)	SND1, NF-κB	Multifunction protein SND1 promotes tumor angiogenesis in HCC via activating NF-κB, consequently in the induction of miR-221, which subsequently induces angiogenesis and CXCL16.	165
MiR-221 Hepatocellular carcinoma and cirrhotic tissues, and the human hepatocellular cell lines HepG2, Hep3B and Huh-7 cells	P53, MDM2	MiR-221 can active the P53/mdm2 axis through suppressing MDM2 and, in turn, P53 activation and DNA hypomethylation contributes to miR-221 high expression that induces HCC.	166
MiR-221 The matched HCC cirrhotic tissues and the human hepatocellular carcinoma cell lines SNU449, SNU398 and Hep3B	CDKN1C/P57, CDKN1B/P27	MiR-221 is high-expressed in 71% of HCCs, has an oncogenic function via the suppression of CDKN1C/P57 and CDKN1B/P27 protein expression.	119
MiR-221 Human HCC cell lines HepG2, SNU398 and Hep3B	P53, Notch3, Cyclin G1, MDM2	Notch3 regulates P53 expression by cyclin G1 in tumor cells and sustained by the miR-221-MDM2 axis in P53 wild type HCC cells upon Notch3 suppression.	167
MiR-221 The hepatoma cell lines SK-HEP-1, HepG2, SMMC-7721 and cervical cancer cell line Hela	BMF, BBC3, ANGPTL2	MiR-221 suppressed the expression of BMF, BBC3 and ANGPTL2 via bound straightly to the 3′-UTR of these targets and subsequent over expression of miR-221 promotes cell proliferation, clonogenicity, migration/invasion in liver cancer cells.	168
MiR-221 and miR-122 Serum samples from HCV-infected patients	–	Circulating miR-221 level is considerably over-expressed in the serum of HCV infected patients.	169
MiR-221 The human HCC-delivered cell lines Hep3B, HepG2 and SNU449 and the human liver tumor tissue specimens and their corresponding paraneoplastic liver (FFPE) tissues	–	The miR-221 level was up-regulated in the metastatic group of HCC compared to the non-metastatic group. As well as miR-221 high expression was relevant to the status of tumor capsular infiltration HCC clinical samples. Also cell growth was suppressed and apoptosis was enhanced through miR-221 inhibitor *in vitro*. So expression of miR-221 in FFPE tissues could be a prognostic biomarker for HCC.	170
MiR-221/222 MEC1 cell line and leukemic lymphocytes from PB, BM or LNs of patients with CLL	P27	MiR-221/222-transducted MEC1 cells plays crucial role to a deregulation of cell-cycle machinery as illustrated by the improvement in the G1/S transition and high expression of both miRNA are consistent with a down-regulation of P27 activity.	121

Table continued

MiR-221 and miR-128b RS4; 11 and SEM cell lines carrying the chromosomal translocation t(4;11)(q21;q23)	CDKN1B	Expression of miR-128b and miR-221 is down-regulated in primary cell samples of MLL-rearranged ALL. As well as the two miRNAs have cooperative effect in inducing drug resistance. MiR-128b down-regulated target genes include MLL, AF4, and both MLL-AF4 and AF4-MLL fusion genes; miR-221 down-regulates CDKN1B.	122
MiR-221 and miR-374 Bone marrow samples from T-cell acute lymphoid leukemia (T-ALL) patients	–	MiR-221 is over-expressed in T-ALL patients with T-ALL/CD56$^-$ and those with T-ALL/CD56$^+$ may require a more crucial monitoring of the response to remedy.	171
MiR-221 and miR-130a Mouse fetal lung endothelial cells (MFLM-91U)	HOXb5, VEGFR2	Anti-miR-221 treatment lungs had more distal branch generation with elevated Hoxb5 and VEGFR2 around airways. Conversely, mimic 221 treatment lungs had decreased airway branching, expanded airways tips and reduced Hoxb5 and VEGFR2 in mesenchyme. Anti-miR-130a treated led to decreased airway branching with elevated Hoxa5 and reduced VEGFR2 in the mesenchyme. Conversely, mimic 130a treatment lungs had numerous well arborized branches into central lung regions with spread localized Hoxa5 and elevated VEGFR2 in the mesenchyme.	130
MiR-221 Plasma of patients with NK/T cell lymphoma	–	Expression level of miR-221 is promoted in the circulation of NK/T-cell lymphoma patients, and an increase plasma miR-221 level is related with a poorer efficiency at baseline and a less favorable long-term consequence.	172
MiR-221/222 The sporadic high grade ovarian carcinomas tissue samples	CDKN1B (P27), CDKN1C (P57)	Up-regulation of MiR-221/222 in ovarian carcinoma may increase proliferation by reducing expression of the cell cycle inhibitors and tumor suppressors CDKN1C (P57) and CDKN1B (P27).	173
MiR-221, miR-99, miR-93, miR-17-5p, let-7b, miR-106a, and miR-92 The MYCN-non amplified neuroblastoma cell line, SK-N-SH-EP	MYCN	Expression of miR-221 was induced by MYCN in neuroblastoma.	174
MiR-221, miR-21, miR-335, miR-124 and miR-375 NB cell lines SH-SY5Y, SH-EP1, BEC(1)n, BE(2)-M17V, BE(2)-C, SK-N-LD, SK-N-HM, SMS-KCN, SMS-LHN, CB-JMN, KCN-83n, KCNs and LA-N-1	–	MiR-21, miR-221 and miR-335, are exclusive to non-tumorigenic NB cell phenotype. MiR-335 preserves the non-neuronal characteristics possibly by blocking neuronal differentiation. MiR-124 expression is exclusive to neuroblastic cells and high expression of this miRNA in NB stem cells induces terminal differentiation with attendant decline in their malignant potential. The expression of miR-375 is related with tumorigenic neuroblastic cell phenotype.	175
MiR-221 MiaPaca-2, Panc-1, and BXPC-3pancreatic cancer cells, human pancreatic duct epithelial (HPDE) cells and formalin-fixed paraffin embedded (FFPE) tumor tissues from patients with pancreatic adenocarcinoma	PTEN, P27kip1, P57kip2, PUMA	High expression of miR-221 and down regulation of its targets, PTEN, P27kip1, P57kip2 and PUMA, are responsible for the aggressive nature of pancreatic cancer. Also non-toxic natural agents cisoflavone mixture G2535 and CDF could down-regulate miR-221 and suppress pancreatic cancer cell proliferation and migration rather due to the induction of, PTEN, P27kip1, P57kip2 and PUMA, that are miR-221 targets and generally inactivated in pancreatic cancer.	176

Table continued

MiR-221 Human pancreatic cancer PANC-1, AsPC-1 and MIAPaCa-2 cells	P27, DR5	Metformin inhibited the expression of miR-221 and caused G1-phase arrest through the high-regulation of P27. Metformin induced the expression of DR5, a receptor of TRAIL, and BIM with a pro-apoptotic function in the downstream of TRAIL-DR5 pathway.	177
MiR-221 Two AI (Androgen-dependent) Cap (prostate cancer) cell lines (PC3 and LNCaP-AI) and one AD (Androgen dependent) human CaP cell line (LNCaP) and blood samples from prostate cancer patients	DVL2	AIPC LNCaP-AI lines promoted miRNA expression compared with ADPC line and that five miRNAs (miR-221, miR-222, miR-21, miR-205, and miR-125b) were high-regulated, while two miRNAs (miR-15a and miR-101) were down-regulated. Also miR-221 elevates neuroendocrine differentiation of LNCaP cells in an androgen-deprived environment. MiR-221 partly regulates the invasive ability of AIPC LNCaP-AI via DVL2. MiR-221 was up-regulated in CaP plasma.	178
MiR-221, miR-21, and miR-141 Blood plasma of prostate cancer patients	_	MiR-21 and miR-221 levels in blood of PCa patients are higher than in healthy controls, while for the miR-141, no difference was observed.	179
MiR-221, miR-21, and miR-141 The malignant prostate tissue samples	_	The expression of one of the three miRNAs, miR-221, is related with prostate cancer recurrence after radical prostatectomy.	180
MiR-221, miR-200c, and miR-182 The prostate cancer tissue specimens	RIMS3	Combinations of multi-biomolecules as a potential biomarker for PCa based on the analysis of miRNA microarray and TCGA datasets revealed that both miR-182 and miR-200c being high-regulated and miR-221 being down-regulated in PCa. Also down-regulation of RIMS3 was present simultaneously with the three recognized miRNAs.	181
MiR-221/222 Human PCa PC-3 and LNCaP cells	SIRT1	MiR-221 and -222 were over-expressed in PC-3 cells compared with in LNCaP cells by reducing SIRT1 expression in PCa. Inhibition of MiR-221/222 expression decreases cell proliferation and migration and increases apoptosis in PCa cells. SIRT1 protein is high-regulated in cells after transfection of miR-221/222 inhibitor.	182
MiR-221/222 Human PCa PC-3 and LNCaP, and U87 glioblastoma cells	NF-κB, C-jun	The ectopic modulation of NF-κB and C-jun, two transcription factors considerably involved in prostate carcinoma and glioblastoma beginning and progression, contribute to oncogenesis, via inducing miR-221/222 transcription.	183
MiR-221/222 The PC3 cellular model of aggressive prostate carcinoma, as compared with LNCaP and 22RV1 cell line models of slowly growing carcinomas	P27kip1	The ectopic over expression of miR-221/222 contribute to the growth and promotion of prostate carcinoma via reducing the tumor suppressor P27kip1.	184

Table continued

MiR-221 The PTC (papillary thyroid carcinoma) tissue specimens and human PTC cell lines (TPC-1 and BCPAP) and human embryonic kidney 293 cells (HEK293T)	TIMP3	MiR-221 could promote cell proliferation and invasive of PTC via inhibiting TIMP3 expression through binding to 3′-UTR region of TIMP3 mRNA.	185
MiR-221 The PTC tissue specimens	BRAF	Over expression of miR-221 is related with aggressive clinicopathologic characteristics inducing advanced disease stage, extrathyroidal invasion, and node metastasis in PTCs. BRAF mutation has also correlation with miR-221, that regulate miR-221 expression via NF-κB pathway.	186
MiR-221 The human papillary thyroid cancer cell lines, TPC-1 and NPA and the normal human thyroid cell line, HT-ori3	–	MiR-221 high-expressed in PTC, and the devised CMV/Gluc-xPT_miR-221 system, that was developed to quantify mature miR-221 in PTC, was detect to be crucial way for monitoring the expression and functions of miRNAs noninvasively.	187
MiR-221/222, miR-10b, and miR-92a Minimally invasive follicular thyroid carcinoma (MI-FTC) tissue specimens	–	The expression of miRNAs belonging to the miR-221/222 cluster, miR-10b and miR-92a were considerably over-expressed in metastatic MI-FTC. MiR-10b indicates potential as a prognostic factor for MI-FTC at an initial operation stage.	108
MiR-221 The human PTC cell line (NPA) and the normal human thyroid cell line (HT-ori3)	HOXB5	MiR-221 high-expressed in PTC drives carcinoma gene expression patterns through directly and indirectly regulating numerous genes, including HOXB5. The bioluminescence imaging system applying CMV/Gluc-3′-UTR of HOXB5 is a crucial tool for noninvasive *in vivo* long-term monitoring of functional targeting of miR-221.	188
MiR-221/222 The long-term thyroid carcinoma cell line (BC PAP) and papillary tumor tissue specimens	HMGB1	The binding of HMGB1 to RAGE increases the expression of miR-221 and miR-222 in primary cultures of excised papillary lesions and in an established papillary cancer cell line (BC PAP), that may interference with the PTEN regulation of the cell cycle.	189
MiR-221/222 The human thyroid carcinoma cell line TPC-1 and Hela cells	P27kip1	Over expression of miR-221 and miR-222 reduced P27kip1 protein levels in thyroid carcinoma and Hela cells in the lack of significant alterations in specific P27kip1 mRNA levels.	107
MiR-17-92 and miR-221/222 clusters GIST (gastrointestinal stromal tumors) and GI-LMS tumor tissue specimens and GIST1 cell line, GIST-882 cell line and GIST-T1-R cell line	KIT, ETV1	High expression of miR-17, miR-20a and miR-222 resulted in the down regulation of KIT expression and ETV1 protein levels in two GIST cell lines. The expression levels of the miR-221/222 and miR-17-92 clusters were considerably lower in GIST compared with GI-LMS.	190
MiR-221/222 Esophageal adenocarcinoma cells (OE33 cell line OE19 cell line) and Telomerase-immortalized normal esophageal squamous cells (EPC1-hTERT)	CDX2	The deregulation of CDX2 was promoted by enhanced levels of miR-221/222 during exposure to bile acids through FXR activation in human esophageal epithelial cells.	191
MiR-221/222 Cervical cancer tissues were obtained from the patients with cervical cancer (all squamous cell carcinomas in IB and IIA) Human cervical cancer cell lines HeLa and siHa cells	ARID1A (AT-rich interactive domain-containing protein 1A)	MiR-221 and miR-222 upregulation partly contribute ARID1A loss in cervical cancer. The miR-221/222-ARID1A axis can modulate proliferation and invasion of cervical cancer cells.	140

Table continued

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