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Review Article

The Roles of MicroRNA-331 Family in Cancers

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Abstract

MicroRNAs (miRNAs) are single-stranded noncoding RNA strands that are involved in various pathological and physiological processes. Even though they do not code for any gene, they regulate gene expression by posttranscriptional modification through cleavage or translational repression of messenger RNA. Many miRNAs (for example, *lethal-7* and miRNA-21) have been found to be involved in the pathogeneses of many diseases including cancers. The miRNA-331 family includes three miRNAs, namely, miRNA-331, miRNA-331-3p, and miRNA-331-5p. Recent studies have revealed that the miRNA-331 family is associated with the pathology of some cancers, including colorectal cancer, leukemia, hepatocellular carcinoma, prostate cancer, pancreatic cancer, breast cancer, melanoma, and lung cancer. Therefore, it is important to have a good understanding about how the miRNA-331 family regulates the pathogeneses of these cancers. In this review, we discuss the pathological and physiological roles of the miRNA-331 family. Understanding how these miRNAs regulate the gene expression levels of their targets and their involvement in cancers may lead to better therapeutic strategies to treat cancers.

Keywords: Cancer, microRNA, noncoding RNA

Introduction

Since the discovery of DNA in 1958 by Francis Crick, it has been known that human genetic information is present in DNA, and that it is responsible for the transcription process to form messenger RNA (mRNA). mRNA acts as the blueprint for the formation of specific amino acid sequences, leading to the production of specific proteins.[1] In the 1960s, noncoding RNAs (ncRNAs) with a close resemblance to mRNA in length and splicing patterns were also discovered. They were found to house classes of RNA transcripts that act as RNA molecules instead of coding for any proteins.[2] Further, it was found that ncRNAs also regulate the transcription and translation processes of protein-coding genes.[1,3,4] Other than small ncRNAs, large ncRNAs have also been discovered in the human genome. An example of a functional large ncRNA is the X-inactive-specific transcript, that is exclusively expressed from an inactive X chromosome and works as a silencing agent for the entire X chromosome in females.[1,5]

Evidence has shown that ncRNAs participate in both physiological and pathological processes. In a normal person, 75% of the human genome is transcribed into RNA with

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only 3% being transcribed into mRNAs with protein-coding elements present within. Hence, ncRNAs are far more abundant than the RNAs of the normal-protein coding genes.[6] Considering the regulatory role and high abundance of ncRNAs in the human body, they are considered to be potential biomarkers or therapeutic targets for various diseases.[7-11] Several types of ncRNAs have been identified, including microRNAs (miRNAs), small interfering RNAs (siRNAs), and Piwi-associated RNAs.[1,12] Among these, the roles of miRNAs have been frequently investigated since the discovery of their involvement in cancer development.[4] In addition, other studies have indicated their involvement in embryonic development and regulation of the immune system.[13,14] miRNAs have gained much attention and recognition due to their roles in epigenetic processes, cellular communication, human physiology, pathology of diseases, and therapies.[1,4,14,15]

miRNA was first identified from the *lin-4* gene of the parasite *Caenorhabditis*.[1,15] It was noticed in *Caenorhabditis elegans* that the *lin-4* gene produces an antisense oligonucleotide complementary to multiple sites present in the 3'-untranslated region (UTR) of the *lin-14* gene; and that through this antisense mechanism *lin-14* was repressed by *lin-4*. These findings triggered further interest in the roles of these complementary sites in the regulation of *lin-14* by *lin-4*.[3] Later, it was found that *lin-4* only regulates *lin-14* at the protein translation, but not at the transcription level. Taken together, it was hypothesized that when *lin-4* RNAs base pair to the 3'-UTR of *lin-14*, a specific translational repression on the *lin-14* gene occurred.[1,3] In 2000, another small regulatory RNA, *lethal-7* (*let-7*) was identified. It was initially observed in the heterochronic pathway of *C. elegans* that is responsible for encoding a ~22 regulatory RNA, and its mechanism is similar to *lin-4* RNA. It plays an important role in the transition of the larval stage of *C. elegans*, in which it allows the parasite to be able to transform from late-larval to the adult stage. Since its discovery, homologs of the *let*-7 gene and even *let*-7 RNA itself have been observed in other species such as fish, mice, and humans.[1,13,16] Later, these single-stranded RNAs, which are usually 19-24 nucleotides in length, were named miRNAs.[1,15] In fact, miRNA is one of the many classes of small ncRNAs present in every location of the genome.[14] Mature miRNAs can silence the respective mRNAs through binding to their partial complementary sequence via an antisense mechanism.[1]

miRNAs regulate the posttranscriptional gene expression.[17] They can be seen in nonprotein-coding regions and even in protein-coding regions, and thus, they can be co-transcribed together with the host genes.[14] The formation of miRNAs is similar to the biogenesis of traditional mRNAs. After transcription, the miRNAs undergo capping, polyadenylating together with splicing to form long primary transcripts. However, in contrast to the mRNA, their active region is located within a ~70 nucleotide hairpin structure. In the early stage, RNA polymerase II situated in the nucleus initiates the formation of long primary transcripts, the pri-miRNAs that originate from the miRNA genes. MiRNA transcripts are known for having a complementary sequence within a characteristic transcript, thus allowing the RNA to be folded into a stem-loop or hairpin-like structure that can be further processed into a mature miRNA.[14,18] This hairpin structure is later cleaved by Drosha and Dicer, the endonuclease enzymes, to generate a short 22-nucleotide ncRNA known as mature RNA that is similar to siRNA.[15] Eventually, this product is assembled into the RNA interference-effector complex, RNA-induced silencing complex (RISC).[1,3,12] The RISC consists of the Argonaute protein, trans-activation response RNA binding protein and Dicer. The Argonaute protein serves to cleave a nonguided strand through endonucleolytic hydrolysis, leaving behind a 5'-phosphate and a 3'-hydroxyl group at the end.[12,18] The RISC is directed by miRNAs to down-regulate gene expressions by either one of two posttranscriptional mechanisms: cleavage of mRNA or translational repression. Consequently, this leads to decreased production of proteins. If the miRNA is highly complementary to the mRNA, a specific cleavage will occur. If no complementary site is present, the translational repression process will take over to suppress any productive translation.[1,13,15] Figure 1 depicts the biogenesis of mature miRNA.

MicroRNAs and Diseases

MiRNAs are often discussed in relation to cancers either as oncogenes or their ability to down-regulate tumor suppressor genes by binding to 3'-UTR of the targeted mRNAs, destabilizing the mRNA, and leading to translational repression.[1,4,19,20] Investigations on the differential expressions and patterns of miRNAs in cancers would provide a better understanding of their physiological and pathological roles in the human body, and enable the potential identification of therapeutic targets for various cancers.[1,13,14] In the past, microRNAs of the *let-7* family have been associated with lung, ovary, cervical, urothelial, and breast cancers. For instance, *let-7g* was identified on 3p21, a region known to be involved in lung cancers. Further, an *in vitro* study showed that *let-7* decreases the proliferation and stops cells in the G1-S transition, and is, therefore, acting as a tumor suppressor gene.[1] Moreover, *let-7* has also been shown to reduce the expression of High Mobility Group AT-Hook 2, an oncogenic high-mobility group protein, and prevent differentiation of breast cancers as well as lung cancers.[1,21] Decreased expressions of the *let-7* family have also been associated with the overexpression of RAS oncogene, leading to a decreased survival rate in patients with nonsmall cell lung carcinoma.[22] In contrast, increased expressions of certain oncogenic miRNAs have been related to increased tumor growth, enhanced chemo-resistance, and down-regulation of apoptosis. For example, miR-21 has been found to be increased in glioblastoma multiforme (GBM) and detected at high levels in aggressive cancers.[1,19,22]

Recent studies have revealed that the miRNA-331 family members, namely, miRNA-331, miRNA-331-3p, and miRNA-331-5p, are associated with the pathology of some cancers, including colorectal cancer (CRC), leukemia,

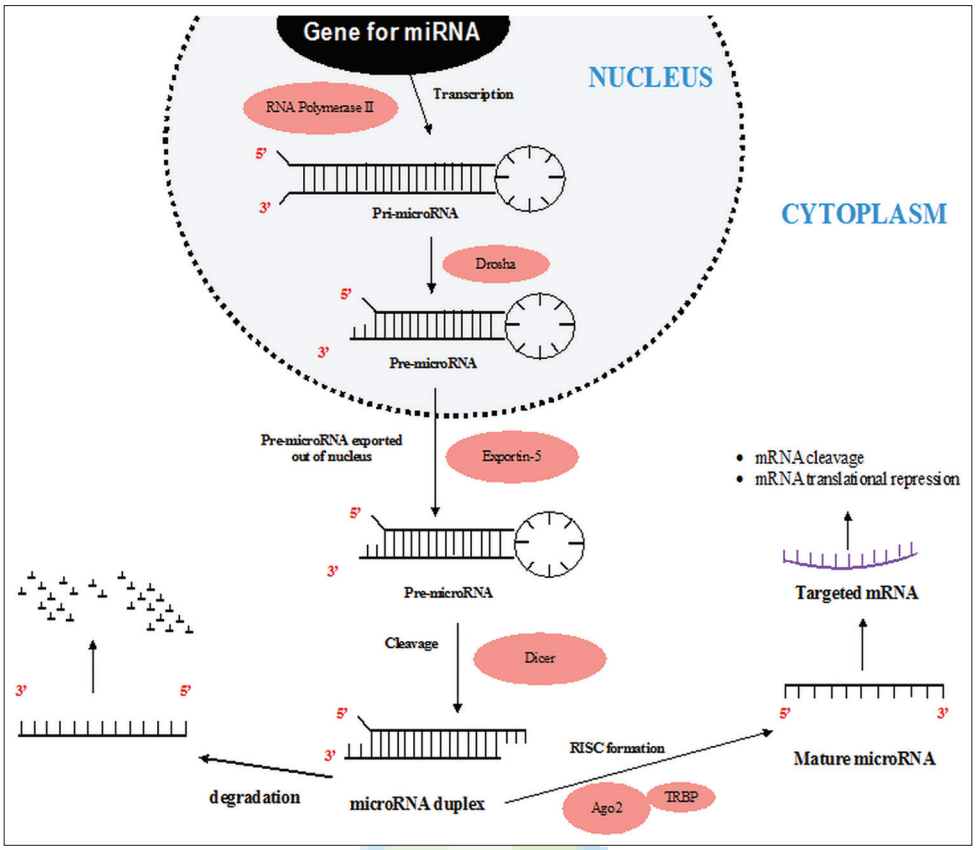

Figure 1: Biogenesis of mature microRNA. The microRNAs gene undergoes transcription by the RNA polymerase II to form the pri-microRNA that will be cleaved into pre-microRNA by Drosha. The pre-microRNA will be then exported out of the nucleus into the cytoplasm by the protein exportin-5. The pre-microRNA will be cleaved by Dicer, to form a MicroRNAs duplex consisting of a passenger strand and a mature microRNAs. The passenger strand will be degraded, whereas the mature microRNAs mediates gene-silencing processes by targeting specific messenger RNAs

hepatocellular carcinoma (HCC), prostate cancer (PCa), pancreatic cancer, breast cancer, melanoma, and lung cancer. Therefore, it is important to have a good understanding about how the miRNA-331 family regulates the pathogeneses of these cancers. Hence, in this review, we discuss the pathological and physiological roles of the miRNA-331 family. Understanding how these miRNAs regulate the gene expression levels of their targets and their involvement in cancers may lead to better therapeutic strategies to treat cancers.

MicroRNAs-331

MiRNA-331 or miR-331 is a miRNA encoded by a gene located at the chromosomal position of 12q22.[23-25] It is known to be involved in solid tumors such as colorectal, leukemia, hepatocellular, and lung carcinoma.[26-30] To date, over 20 studies have reported altered expression levels of miRNAs in CRC. A previous microarray study reported that the expression of miRNAs in CRC was significantly different from that in nonneoplastic tissue.[31] Due to the possible involvement of miR-331 in CRC, Kanaan *et al.* proposed that it might be a potential biomarker which could be used to distinguish adenomas from CRC.[28]

MiR-331 has also been reported in studies of acute lymphocytic leukemia, chronic myeloid leukemia, and acute myeloid leukemia (AML).[26,27] The miRNA has also been found to be involved in the down-regulation of suppressor of cytokine signaling, leading to increased cell proliferation.[27] Butrym *et al.* found that miR-331 was overexpressed in AML patients and that this overexpression was associated with a low-survival rate and also a poor response to chemotherapy. On the other hand, the miR-331 expression level was decreased in patients who had successful therapy, indicating that miR-331 is probably pro-oncogenic in nature.[26]

Another study showed that miR-331 was up-regulated in rat HCC.[30] This miRNA was also involved in lung adenocarcinoma (LUAD). It has also been reported that miR-331 might be useful as an independent prognostic marker in predicting the survival of LUAD patients for up to 5 years, regardless of the smoking history of the patients. The miRNA enables identification of those who are more prone toward the recurrence of LUAD. However, this study was limited by not taking into consideration adjuvant therapy received by the patients,[29] and adjuvant therapy might have altered the miRNA expression and interfered with the outcome of the study. Hence, it is advisable that any future studies should include the detailed clinical history of the patients. Sierzega *et al.* also demonstrated that miR-331 was overexpressed in gastric cancer, and that it was detected at a higher level in peripheral blood compared

to the primary tumor vein, suggesting a localized alteration in miR-331 expression level in the tumor.[32]

A recent study also reported that, miR-331 was overexpressed in malignant breast tumors. Further analysis also revealed that the level of miR-331 might provide valuable information for the differential diagnosis of benign and malignant breast tumors.[33] In addition, another study also found that miR-331 was underexpressed in melanoma, and the overexpression of miR-331 has been reported to inhibit cell proliferation and invasion, probably by targeting AEG-1 and regulating the phosphatase and tensin homolog/protein kinase B (AKT) signaling pathway.[34]

MicroRNAs-331-3p

MiR-331-3p is a member of the miRNA-331 family, with a length of around 21 nucleotides.[25] MiR-331-3p has been shown to be involved in cancers such as PCa, cervical cancer, glioblastoma, CRC, and HCC.[32,35-42]

PCa is the adenocarcinoma of prostate that is caused by a genetic mutation that activates the oncogenic phosphoinositide 3-kinase (PI3K)/Akt signaling pathway.[35] The overexpression of Erb-B2 receptor tyrosine kinase 2 (ERBB-2), commonly referred to as human epidermal growth factor receptor 2 (HER-2 or HER-2/neu), can lead to the activation of the PI3K/Akt pathway which triggers androgen receptor signaling in hormone-independent PCa. In 2009, Wang *et al.* demonstrated that miR-331-3p could induce apoptosis in PCa cells leading to growth arrest.[36] Similarly, Epis *et al.* demonstrated that miR-331-3p acts as a tumor suppressor by down-regulating the expression of ERBB-2 in PCa.[37] They proposed that the tumor-suppressing effects of miR-331-3p in PCa are associated with deoxyhypusine hydroxylase (DOHH) and eukaryotic translation initiation factor (eIF5A). DOHH is an enzyme responsible for catalyzing eIF5A and cell growth, and it has been found to be overexpressed in several PCa cell lines. It is likely that the overexpression of miR-331-3P in PCa cells decreases the expression of DOHH, and hence, stops cell proliferation.[22]

MiR-331-3p has been found to down-regulate HER-2 in breast cancer cells.[38] In addition, miR-331-3p has also been associated with gastric cancer. A long ncRNA, Hox transcript antisense intergenic RNA (HOTAIR) was shown to be up-regulated in gastric cancer in one study, and when miR-331-3p was added to the cancer cells, it was found that the expression level of HOTAIR was greatly reduced. In addition, results from a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay showed that gastric cancer cells transfected with miR-331-3p suffered from growth retardation, suggesting that miR-331-3p was antiproliferative to the cancer cells.[39] In another study, miRNA-331-3p was found to be involved in PCa and glioblastoma by regulating the expressions of epidermal growth factor receptor and HER-2 via reducing Akt activity.[18] MiR-331-3p has also been demonstrated to affect GBM by inhibiting the expression of neuropilin 2 (NRP-2), a receptor responsible for tumorigenesis, and that this can lead to decreased GBM cell proliferation.[19,40] Similarly, the overexpression of miR-331-3p has been shown to suppress NRP-2 in cervical cancer cells, leading to the G_2/M phase arrest followed by apoptosis.[41] Zhao *et al.* showed that miR-331-3p also participates in CRC. In addition, when miR-331-3p down-regulates HER-2 in colon cancer cells, it deactivates PI3/Akt as well as extracellular signal-regulated kinase 1/2 signaling pathways, thus acting as a tumor suppressor.[42]

MiR-331-3p has also been observed to play a role in HCC. According to an experiment performed at the Third People's Hospital of Nantong City, the level of miR-331-3p detected in the serum of HCC patients was significantly higher than that in control and benign groups, indicating its potential as a cancer biomarker.[43] Cao *et al.* suggested that the overexpression of miR-331-3p can actually lead to liver cancer cell proliferation and metastasis because miR-331-3p can target the Pleckstrin homology domain and the leucine-rich repeat protein phosphatase that is responsible for the proliferation and metastasis of cancer cells. They also found that miR-331-3p is probably overexpressed in the presence of hepatitis B virus (HBV). MiR-331-3p works through targeting the inhibitor of the growth 5 (ING5) gene which is a tumor suppressor gene. Their study showed that HBV probably upregulates the expression of miR-331-3p, subsequently inhibiting the ING5 gene. However, the findings were not conclusive, as the action of miR-331-3p on ING5 may be triggered by not only HBV but also by more yet unidentified factors.[44] Hence, more studies are still required to have a better understanding of the mode of action of miR-331-3p. Figure 2 summarizes the molecular network in which miR-331-3p is critically involved in cancers.

A very recent study also revealed an association between miR-331-3p and pancreatic cancer. In that study, miR-331-3p

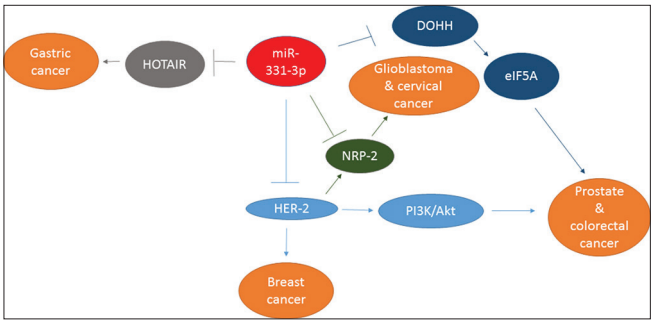

Figure 2: Molecular network in which miR-331-3p is critically involved in various cancers. Overexpression of human epidermal growth factor receptor 2 is associated with breast cancer cell growth. It also leads to the activation of phosphoinositide 3-kinase/protein kinase B pathway and increased level of neuropilin which promotes the growth of prostate, colorectal and cervical cancers as well as glioblastoma. MiR-331-3p inhibits the growth of the cancer cells by inhibiting the expressions of human epidermal growth factor receptor 2 and neuropilin 2. Deoxyhypusine hydroxylase catalyzes eukaryotic translation initiation factor that is responsible for prostate cancer cell growth. Inhibition of deoxyhypusine hydroxylase by miR-331-3p stops the prostate cancer cell proliferation. MiR-331-3p inhibits gastric cancer growth by downregulating Hox transcript antisense intergenic RNA

was found to be tumor-promoting by targeting the gene of suppression of tumorigenicity 7 like, of which the gene sequence is highly similar to the ST7 tumor suppressor gene located at the chromosome 7q31 region, in pancreatic cancer cells.[45]

MicroRNAs-331-5p

MiR-331-5p is also a member of the miR-331 family, with a length of around 22 nucleotides.[25] Its association with cancer was first mentioned in leukemia. It has been reported that the down-regulation of miR-331-5p is related to the overexpression of P-glycoprotein that can lead to anti-cancer drug resistance to doxorubicin.[46,47] While the level of miR-331-5p is normally lower in cancer relapse patients with lymphocytic and myeloid leukemia, the overexpression of the miRNA has actually been shown to have a protective role by increasing drug sensitivity of the leukemic cells, thus inhibiting cancer drug resistance and preventing cancer relapse.[47]

Recently, Zhan *et al.* demonstrated the involvement of miR-331-5p in lung cancer.[48] It has also been found that miR-331-5p regulates the mitogen-activated protein kinase (MAPK) pathway that is responsible for tumor invasion, and also that it targets transforming growth factor beta 2 that is responsible for the metastasis of lung cancer. The role of miR-331-5p in nonsmall cell lung cancer was also confirmed in one study, in which circular RNA circ_0001649 was found to act as a sponge for miR-331-5p to inhibit the progression of nonsmall cell lung cancer.[49] When administered with curcumin or diferuloylmethane, a natural compound extracted from the spice turmeric (*Curcuma longa*) that is supposed to be chemopreventive agent in various types of cancer, it was found that the MAPK pathway was down-regulated.[50,51] However, due to limited available information, the effects of curcumin in the regulation of miR-331-5p are still remain unknown, and thus, there is a need for further detailed studies.[50]

Apart from its association with cancers, miR-331-5p was also mentioned in a study about Parkinson's disease (PD). In that study, miR-331-5p was found to be a possible biomarker for PD. The study identified 384 miRNAs in the sera of PD patients and found that the expression of miR-331-5p was 21-fold higher in the patients than in the healthy controls. By using bioinformatics tools for gene analysis, it was predicted that the genes involved had the target sites of miR-331-5p in the 3'-UTR. Due to the limited number of patients in the study, the pathological roles of miR-331-5p remain elusive. Future studies should include a larger number of patients, preferably in different stages of PD. More studies are also needed to fully understand its mechanisms of action as well as its physiological or pathological roles.[52]

Conclusion

In summary, the miRNA-331 family, including miRNA-331, miRNA-331-3p, and miRNA-331-5p, have been widely researched in cancer studies. MiRNA-331 has been shown to be involved and overexpressed in colorectal, leukemia, hepatocellular and lung carcinomas, whereas miRNA-331-3p has been shown to be involved in PCa, cervical cancer, glioblastoma, CRC, and HCC. Moreover, miRNA-331-5p has been associated with leukemia and lung cancer, as well as PD. Given that this family of miRNAs is involved in many types of cancers, its role in the pathogenesis and pathology of cancers should be further investigated.

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Conflicts of interest

There are no conflicts of interest.

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