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miRNA-141 as the Biomarker for Human Cancers

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Abstract

microRNA (miRNA) is considered to be a pivotal role in human numerous biological process, and their abnormal expression that functions either as tumor suppressor or oncogenes results in human cancer initiation and development microRNA-141 (miR-141), belonged to the miR-200 family, located at 12p13.31 and is also found to be abundantly expressed in many human cancers. Additionally, Prognostic and predictive miR-141 signatures have been defined for a variety of cancer types. This review summarized the biogenesis and processing of miRNA, as well as the roles of miR-141 in human cancer pathways, its targets and the potential utility of miR-141 as prognostic biomarkers.

Keywords: Biomarker, Human Cancer, microRNA, microRNA-141

1. Introduction

microRNAs (miRNA, miR), originally discovered in Caenorhabditis elegans are the small class of endogenous, functional non-coding RNAs, and highly conserved and widely found in animals, plants, protists, viruses (represents ~20 nucleotides)[1–4]. miRNA regulates gene expression by binding to sequences in 3'-untranslated region (3'-UTR) of their target mRNAs, resulting in the repression and/or degradation of mRNA, proven to be associated to a wide range of biological processes such as cell division, proliferation, differentiation, apoptosis, metastasis, stress responses etc[1,5–7]. In the past decades, growing evidences indicated that miRNAs have been implicated as both oncogenes and tumor suppressors that the abnormal expression (positive regulation or downregulation) of miRNAs contributes to various human tumor pathogenesis[3,7–11]. This current review is aimed to summarize the biogenesis and processing of miRNA, as well as the roles of miR-141 in human cancer pathways, its targets and the potential utility of miR-141 as prognostic biomarkers.

2. Biogenesis and Processing of miRNAs

Mature miRNA is generated via two-step cleavage of primary miRNA in both nuclear and cytoplasmic. The most of miRNA-coding genes are located in the introns of protein-coding genes, and the introns or exons of non-coding genes[12]. In canonical pathway, miRNAs are mainly transcribed by RNA polymerase II (RNA pol II)-dependent from their own promoter or the promoter of the host genes in which they inside, and its controlled by RNA pol II-associated transcription factors and epigenetic regulators[13,14]. Resulting in synthesis of large miRNA precursors called primary miRNA (pri-miRNA), which contains local hair-spin structure, that varies from hundreds to thousands of base pairs in length[13–15]. The 5'7 methyl-guanosine capped and 3' polyadenylated miRNA are cleavage at the stem of hair-spin structures, releases a ~60-70 nucleotide hair-spin structure termed the precursor miRNA (pre-miRNA). This process takes place in nucleus and catalyzed by the microprocessor, con-

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tains the nuclear RNase III-type protein Drosha and its cofactor DiGeorge syndrome critical region 8 (DGCR8) protein in human (or Pasha protein in Drosophila melanogaster and Caenorhabditis elegans)[16]. The pre-miRNA, then, is exported into the cytoplasm for further processing through the mediation of Exportin-5 (EXP 5), also originally known as a minor export factor for tRNAs, and Ras-Related Nuclear Protein Guanosine Triphosphate (RAN-GTP)[17]. Following export from the nucleus, the terminal loop of pre-miRNA is removed by RNA III Dicer and its cofactor Transactivation-Responsive RNA-Binding Protein (TRBP), releasing ~20-22 nucleotide miRNA-duplex, contains two 5' phosphorylated sequence strands with 3' overhangs, named as mature miRNA guide strand and complementary passenger strand[15,18]. Subsequently, the miRNA-duplex loaded into an Argonaute protein (Ago protein) so as to generate the effector complex, termed the RNA-Induced Silencing Complex (RISC). The mature miRNA, also known as miRNA, preferentially derived from the guiding strand, remains in Ago, whereas the complementary passenger strand is degraded. Mature miRNA bound to the miRNA-Induced Silencing Complex (miRISC), that participates in the regulation of gene expression through binding to the target mRNAs leading to the degradation of mRNA (in case of perfect pairing between the miRNAs-mRNA target pairing) or the blocking of mRNA translation (in case of imperfect pairing)[10,19].

2.1 miRNA-141

miR-141, clustered with miR-200c, located at 12p13.31 (nt: 6964097-6964191, [+]), is belonged to the miR-200 family. The miR-200 family concludes five subfamilies, miR-200a, miR-200b, miR-200c, miR-141, and miR-429, which classified based on the sequence homology in their seed regions (Figure 1). The first subfamily group concludes miR-141 and miR-200a with the homologous sequence "AACACUG", the second one composed by miR-200b, miR-200c, and 429 with the homologous sequence "AAUACUG".

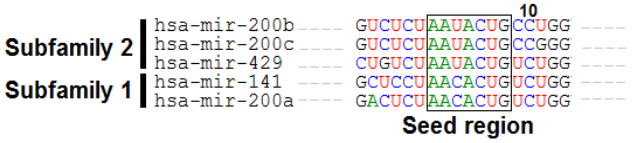

Figure 1. Two subfamilies of miR-200 family. Sequences of the five members of miR-200: miR-200a, miR-200b, miR-200c, miR-141, and miR-429family were collected from miRNA database (http://www.mirbase.org) by following accession numbers: MI0000737, MI0000342, MI0000650, MI0000457, and MI0001641. The alignment was done by BioEdit Sequence Alignment Editor software.

Corresponding to current release of miRNA database (http://www.mirbase.org), the mature miR-141 composes two mature sequences, termed hsa-miR-141-5p (has-miR-141*) and hsa-miR-141-3p (has-miR-141)

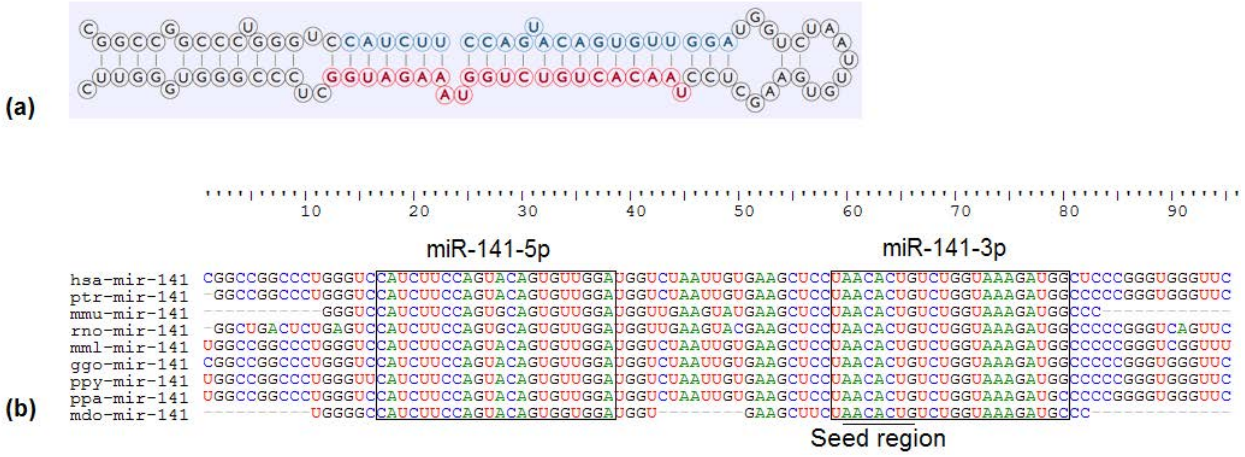

Figure 2. **(a)** The schematic representation of the hairpin structure of the pre-miR-141. The mature of miR-141-3p (the guiding strand) is indicated in red. The miR-141-5p (the complementary passenger strand, previously termed miR-141*) is indicated in blue; **(b)** The highly conserved nucleotides of miR-141 is observed in many species: ptr: *Pan troglodytes*; hsa: *Homo sapiens*; mmu: *Mus musculus*; rno: *Rattus norvegicus*; mml: *Macaca mulatta*; ggo: *Gorilla gorilla*; ppy: *Pongo pygmaeus*; ppa: *Pan paniscus*; mdo: *Monodelphis domestica*.

(Figure 2(a)), and showed the highly conversed in many species (Figure 2(b)).

2.2 miR-141 Functions as Both Tumor Suppressor Gene and Oncogene to Regulate Human Cancers

2.2.1 Functions of miR-141 Expression in Various Human Cancers

Up to date, a great deal of researches demonstrated miRNAs expression is a defining trait of tumorigenesis: Amplification or overexpression of miRNAs could act as the tumor suppressor genes, that downregulates different proteins with oncogenic activities; they act as the oncogenes, that suppresses the activities of tumor suppressor genes leads to the over proliferation, angiogenesis and invasion[19,20]. An interesting case is presented bymiR-141, which was associated to human various cancers, including nasopharyngeal carcinoma[5,20], hepatocellular carcinoma[21–23], colon cancer[24,25], prostate cancer[26–28], bladder cancer[28,29], ovarian cancer[30–32], breast cancer[34–36] etc. Considering to the role of miR-141, it is suggested to possess the dual roles in human tumorigenicity: functions as both oncogenic or tumor suppressive roles in human malignancies (Table 1).

2.3 Tumor Suppressor miR-141

A great deal of researches has been carried out to find out the role of miR-141 in human malignancies. The deregulated miR-141was screened out in various human cancers and suggested to be tumorigenesis activities. For instance, previous studies reported that miR-141 was downregulated in Hepatocellular Carcinoma (HCC), Renal Cell Carcinoma (RCC), Gastric Carcinoma (GC). In this case, Wu et al. (2014)[22] reported that the expression of miR-141 was significant decreased in 4 HCC cell lines, includes HepG2, SMMC-7721, Huh7, and QGY-7703[22]. In their research, they found that the expression of miR-141 suppressed both the growth and the motility of HCC cells by targeting the Zinc finger E-box Binding homeobox 2 (ZEB2) gene through the binding between the binding sites of miR-141 and the ZEB2 3′-UTR (Figure 3). *ZBB2* gene is a member of the δEF-1 family (or ZEB family) of two-handed zinc finger nuclear factors, which encoded protein, ZEB2, a transcriptional factor that that involves in many signaling pathways[37]. The expression of ZEB2 has so far been reported in many human cancers by induced the Epithelial to Mesenchymal Transition (EMT) through the inhibition of the expression E-cadherin as well as other genes coding for crucial proteins of tight junctions, desmosomes, and gap junction, leads to the promotion of tumor progression and metastasis[22,37]. Additionally, consistent with the results of Wu et al.,[22] study, they also found that the expression of miR-141 suppresses the cell proliferation, migration and invasion of HCC cell by targeting the *Tiam1* which was shown to act as a metastasis-related gene in a variety of cancers. miR-141 also could inhibit the proliferation and invasion and promote the apoptosis of HepG2 cell by silencing *HNF*-3β[23]. Therefore, miR-141

Table 1. Dysregulation of miR-141 in many various human cancers

Types of cancer	Expression of miR-141/ role	Target genes	Involved pathway	Reference
Nasopharyngeal carcinoma	Upregulation/ Oncogene	BDR3, PTEN, UBAP1	Rb/E2F, JNK2, PTEN/AKT	5, 20
Colon cancer	Upregulation/ Oncogene	MAP2K4; SIP1	miR-141-MAP2K4; ZEB1/SIP1	25
Prostate cancer	Upregulation/ Oncogene	KLF9, shp	miR-141-3p/KLF9	28, 34
Bladder cancer	Upregulation/ Oncogene			29, 30
Ovarian cancer	Upregulation/ Oncogene	KEAP1, p38α	NF-kB, Nrf2	31, 32, 33
Hepatocellular carcinoma	Downregulation/ tumor suppressor	ZEB2, Tiam1, HNF-3 β,	HNF-3β	21, 22, 23
Renal cell carcinoma	Downregulation/ tumor suppressor	EphA2	EphA2/p-FAK/p-AKT/MMPs	38, 39
Breast cancer	Downregulation/ tumor suppressor	ANP32E, PR, Stat5a		34, 36
	Upregulation/Oncogene		FAK and PI3K/AKT	35

was highlighted the importance of role as the tumor suppressor in HCC via the suppressing of many target genes, such as *ZEB2*, *Tiam1*, *HNF-3β*.

The downregulation of miRNA was also found in Renal Cell Carcinoma (RCC)[38,39]. In details, on the research of Chen et al.[39], a total of 74 miRNAs were dysregulated in renal cell carcinoma compared with normal tissue, they found that, in the case of miR-141, it was remarkably downregulated in RCC tissue (counting for 92.6%) and concluded would serve as a promising biomarker for discriminating RCC from the normal tissue with the area under the receiver operating characteristics curve of 0.93. Moreover, they also found that miR-141 plays a crucial suppressor role in RCC development and metastasis by targeting erythropoietin-producing hepatocellular A2 (EphA2) through modulating the EphA2/p-FAK/p-AKT/MMPs signaling cascade. These results indicated miR-141 was downregulated, functioning as a tumor suppressor by inhibit the cell proliferation, migration as well as invasion of cancer cells.

2.4 Oncogenic miR-141

Among previous studies, miR-141 was reported to play an oncogenic role in human malignancies. For instance, miR-141 was found to be significantly upregulated in Nasopharyngeal Carcinoma (NPC) specimens in comparison with normal nasopharyngeal epithelium by qRT-PCR[20]. They then found that miR-141 plays oncogenic activities to effect the cell proliferation, migration and invasion through positively regulated the Rb/E2F and AKT pathway by targeting BRD3, PTEN, UBAP1. The Rb/E2F pathway is essential for the normal cell cycle in which cell progression transfer phase G1 into phase S[40]. The AKT pathway plays an important role in the activation of cascade of different target proteins that involved in the cell growth, proliferation and migration. The phosphorylation of AKT is negative regulated by PTEN, which was identified as a tumor suppressor gene, plays a key role in plays an important role to result in the activation of cascade of different protein targets involved in cell growth, proliferation and invasion, and promote tumorigenesis[20]. According to the research of Zhang et al.,[20] the expression of miR-141 may increase the phosphorylation of AKT via the inhibition of PTEN expression. BDR3, plays a role in the regulation of transcription, probably by chromatin remodeling and interaction with transcription factors, has been also reported as negative regulator of Rb/E2F pathway. Moreover, the tumor-related gene c-MYC, SPLUNC1 may also constitute network to contribute NPC development. Therefore, miR-141 plays a role as an oncogene to affect NPC cell cycle, migration and invasion by positive regulation of Rb/E2F and AKT pathway (Figure 4). The upregulation of miRNA was also observed in colorectal carcinoma. The expression levels of miR-141 were significantly upregulated in clinical samples of colonic adenocarcinoma compared to non-cancerous tissue samples[25]. Moreover, they also found that the overexpression of miR-141 resulted in cell proliferation of CAC by inhibiting MAP2K4 activity. The upregulation of miR-141 has been described in many types of human tumors, such as colon cancer, ovarian cancer, bladder cancer, etc.

The dysregulation of miR-141 expression occurs in multiple types of human cancers, that miR-141 plays a dual role in human tumorigenicity, functioning either as a tumor suppressor gene or oncogene.

2.5 Circulating miR-141 is served as Prognosis and Diagnosis Biomarkers for Cancers

Finding the capable biomarker, which is required to be stable, easily accessed in samples, for cancer prognosis and diagnosis has become a necessary work to increase the rate of patients' survival. Since the discovery of the first miRNAs in 2007, up to date, the dysregulation of miRNAs has been shown in many human tumorigenesis, thus, the analysis of miRNAs features may enable a better prediction of the cancer development[41]. In recent years, the expression of circulating miRNA has been detected in a variety of body fluids such as plasma, serum, saliva,

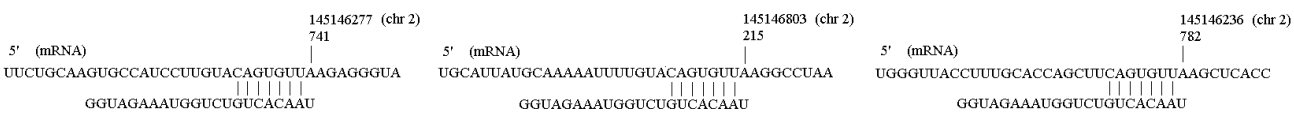

Figure 3. Schematic diagram of three potential binding sites of miR-141 in the ZEB2 3′-UTR (ENSG00000169554). The potential targets of miR-141 (hsa-miR-141-3p) were analyzed by miRmap (http://mirmap.ezlab.org).

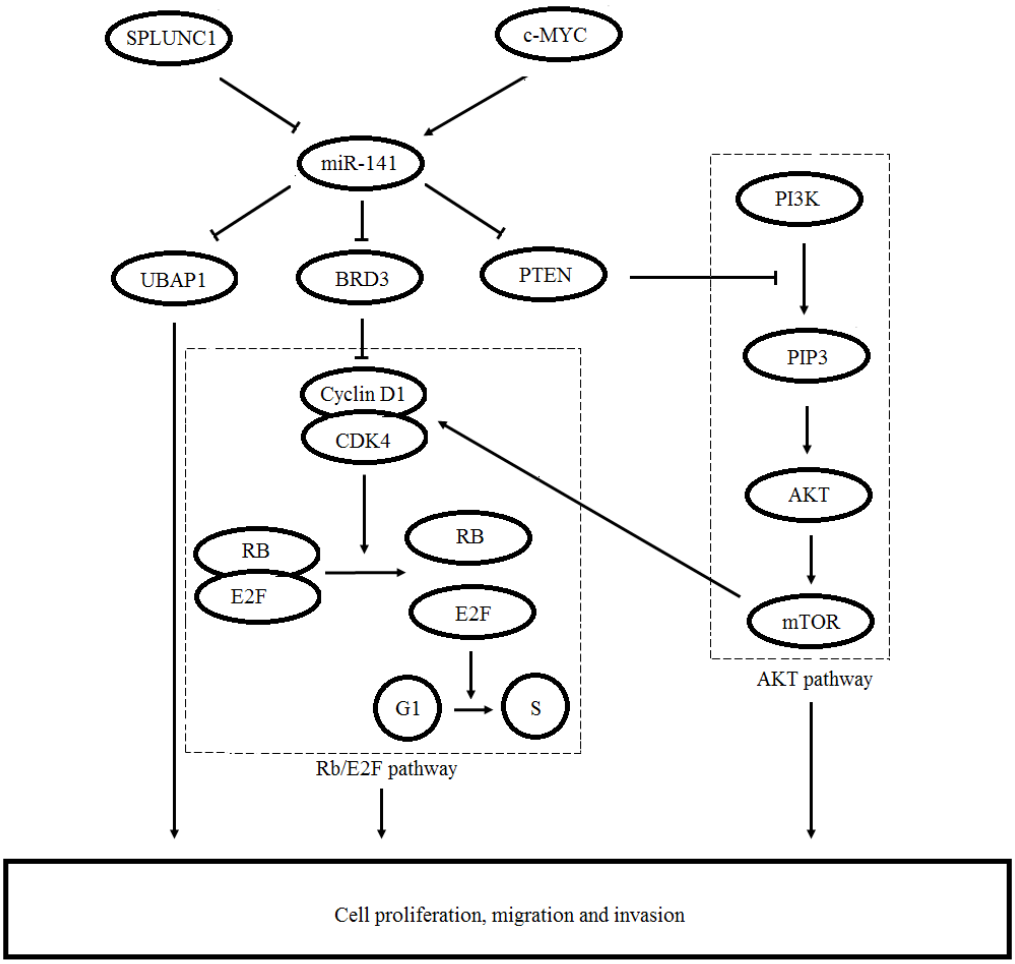

Figure 4. Signaling pathway of miR-141 related to NPC.

etc. and has been used as the potential biomarker in many human diseases, including cancers[42,43]. The use of miRNA seems to be more advantageous due to the stability of miRNAs in body fluids as well as the origin of miRNA[42,43]. Circulating miRNA, directly released by cancer cells, has been reported that they could pass the between cells or tissues and organs through blood circulation, bound to ribonucleoprotein complexes or in extracellular vesicles, such as micro-vesicles, exosomes or apoptotic bodies, which provides the protection from nuclease present abundantly in the body fluids, thus, making them highly stable and resistant to bedegraded[44,45]. These characteristics make miRNAs to be the potential and valuable as novel biomarkers for cancer diagnosis and prognosis.

In the case of miR-141, for instance, Brase et al.,[27] studies about the potential clinical relevance of miRNAs in serum (in total of screening 667 miRNAs, including miR-141) from prostate cancer patients. In their research, miR-375, miR-141, and miR-200b were shown the significant correlation with clinical parameters, such as Prostate-Specific Antigen (PSA). Significantly, both miR-375 and miR-141 were indicated a better performance for discrimination of patients with high-risk tumors (Gleason score 7 ≥ 8) from those with Gleason score 7 prostate cancers[27]. These results were also to be agreed with the conclusion of Mitchell et al.,[46] that circulating miR-141 (serum levels of miR-141) could distinguish between patients with metastatic prostate cancer and healthy controls[46]. The miR-141 was also acted as potential biomarker of therapeutic response in prostate cancer patients[47]. In their study, it was designed to compare the clinical valuable markers, such as Prostate-Specific Antigen (PSA), Circulating Tumor Cells (CTC) with miR-141 and compared miR-141 val-

ues in response to prostate cancer treatment. As the results, a significant correlation between clinical course and miR-141 levels was observed; additionally, logistic regression modeling of the probability of clinical progression demonstrates that miR-141 levels predicted clinical outcomes with an odds ratio of at least 8.3. They concluded that a strong correlation between clinical course and miR-141 levels; thus, it potentially could be a useful tool for evaluating prognosis or treatment efficacy, and perhaps the full utility of miR-141 could be in a combinatorial, multivariate panel with other validated markers. Circulating MiR-141 has also reported to be a potential biomarker for the molecular diagnosis and prognosis in many human cancers, such as ovarian cancer[45,48], Colorectal cancer[49] etc. Thus, the circulating miR-141 may represent a novel biomarker for diagnosis and prognosis in various human cancers.

3. Conclusion

In this review, we highlighted the biogenesis of miRNA, as well as the roles of miR-141 in many human cancers. Additionally, the dysregulation of miR-141 represented easily detectable biomarkers to predict and prognosis human cancers. The further insight of the biological effects of miRNA as well as miR-141 provides our understanding of this processing of complex malignancy to provide more useful prognosis biomarkers and novel therapeutic targets for human cancer treatment in the future.

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5. Author's Contribution

Thuan LD 40%; Phuong TK 30%; Thuy LHA 30%. All authors read and approved the final manuscript.

6. Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study

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9. List of Abbreviations

3'-UTR: 3'- Untranslated Region;
Ago protein: Argonaute Protein;
DGCR8: DiGeorge Syndrome Critical Region 8;
EMT: Mesenchymal Transition;
EphA2: Erythropoietin-Producing Hepatocellular A2;
EXP 5: Exportin-5;
GC: Gastric Carcinoma;
HCC: Hepatocellular Carcinoma;
miR-141: microRNA-141;
miRISC: miRNA-induced Silencing Complex;
NPC: Nasopharyngeal Carcinoma;
pre-miRNA: Precursor miRNA;
pri-miRNA: Primary miRNA;
RAN-GTP: Ras-related Nuclear Protein Guanosine Triphosphate;
RCC: Renal Cell Carcinoma;
RISC: RNA-Induced Silencing Complex;
TRBP: Transactivation-Responsive RNA-Binding Protein;
ZEB2: Zinc Finger E-box Binding Homeobox 2.