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Review Article

Pivotal role of microRNA-138 in human cancers

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Abstract: Aberrant expression of certain microRNAs (miRNAs) has been implicated in cancers as a promising druggable target due to the fact that a modulation of the deregulated single miRNA seems to revert the therapeutically unfavorable gene expressions in cancer cell by targeting multiple genes. Global miRNA profiling from a number of patient cohorts in various type of human cancers has identified miR-138 as a signature of tumor suppressor that are down-regulated in most types of human cancer. As a tumor suppressor, miR-138 can inhibit oncogenic proteins by directly bind to their mRNAs. However, in rare cases of cancer stem cell population from glioblastoma, miR-138 seems to be down-regulated and plays an oncogenic function. This review will summarize accumulating evidence that has shown the expression and functional role of miR-138 in various human cancers with its target genes and pathways in a hope to find a better therapeutic option to treat human cancers.

Keywords: MicroRNA, miR-138, cancer, tumor suppressor, oncogene, glioblastoma

Introduction

Cancer is a complex disease caused by genetic abnormalities. Although cancer has been extensively studied over decades through the lens of tumor-suppressor genes and oncogenes, current understanding on its molecular level of tumorigenesis, progression and metastasis to identify genetic markers are still not sufficient to win the battle. Those genetic markers that are clearly related to cancers can be used not only as diagnostic or prognostic markers but also druggable targets for the development of new therapeutics.

MicroRNAs, approximately 23 nucleotides in length, are the smallest member of noncoding RNA molecules that play key roles in regulating the expression of coding genes [1]. Since the discovery of miRNAs and its involvement in all stages of cancer: tumorigenesis, progression and metastasis, a push for miRNA research in medical science has drawn a great attention from cancer researchers in a hope to find a new therapeutic target. Currently, it has been claimed that approximately 60% of human gene expressions are regulated by miRNAs [1, 2]. In cancer cells, a number of different pathways have been shown to be involved with miRNAs, including cell proliferation and apoptosis [3], differentiation [4], cancer cell metabolism [5] and cell cycle [6]. Due to their crucial roles in controlling diverse metabolic and cellular biological processes, any dysregulation of genetic information could potentially develop into cancers. First miRNA was discovered in *Caenorhabditis elegans* by Victor Ambros laboratory as small RNAs transcribed from the gene lin-4 [7]. They found that both short and long (22 and 61 nucleotides in length) RNAs negatively regulates the lin-14 gene *via* attachment to the 3' untranslated region (3' UTR) region [7, 8]. Shortly after, a similar finding of a small RNA molecule transcribed from the let-7 gene in *C. elegans* [9]. These findings led to the classification of these short RNA molecules as small temporal RNAs (stRNAs) [10], which were later termed miRNAs through the discovery of additional regulatory RNAs [2]. Since then, many miRNAs have been identified in variety of organisms including human and catalogued. Seminal finding in cancer biology was reported in 2002 by Carlo Croce laboratory, in which they found that miR-15/16 cluster is frequently deleted in

chronic lymphocytic leukemia (CLL) patients as tumor suppressive players since the miR-15/16 can negatively regulate oncogene BCL2 expression [11]. This first pathological evidence that miRNAs are directly linked to human cancer development and progression has stimulated extensive studies on miRNAs in human cancers, and led to countless findings showing specific targeting of coding genes by specific miRNAs [12].

Biogenesis of miRNA

In order to effectively use those miRNAs as potential biomarkers and/or therapeutics, understanding the mechanism of miRNA biogenesis is critical. Mature form of miRNA is generated through a two-step cleavage of a long primary miRNA (pri-miRNA) after transcribed by RNA polymerase II [13]. The pri-miRNA is then processed by Drosha, a nuclear RNase III molecule, into a shorter ~70 nt hairpin structure, called a precursor miRNA (pre-miR) [14]. A nuclear membrane channel protein Exportin-5 (EXPO5) then transports the pre-miR into the cytoplasm [15], which is further cleaved again by a Dicer enzyme, creating a mature miRNA [16]. From there, the miRNA forms an RNA-induced silencing complex (RISC) and is guided to the 3' UTR of target mRNA. The resulting miRNA/mRNA complex inhibits the ribosomal complex responsible for protein synthesis, effectively inhibiting the translation of gene expression [17]. Due to the nature of partial complementary binding between the 3' UTR and the seed sequences of miRNA, the mature miRNA can bind to hundreds of distinct mRNA target strands [1]. It makes it extremely versatile and effective during the function of miRNAs in gene regulation processes. Furthermore, miRNAs have also been identified to irreversibly initiate mRNA degradation *via* deadenylation, which trumps the inhibition of translation by miRNA [18, 19].

MicroRNA-138 (miR-138) in human cancers

MiR-138 originates from two primary transcripts, pri-miR-138-1 and pri-miR-138-2 as encoded on chromosomes 3 (3p21) and 16 (16q13) which form the mature miR-138 [20, 21]. The expression level of miR-138 was found to be regulated by many different epigenetic mechanisms. For examples, DNA hypermethylation of miR-138 promoter is negatively correlated with miR-138 expression in breast cancer [22]. Some of transcription factors, such as p53, HOXA4 and GATA1, were also shown to regulate the expression of miR-138 in non-small cell lung carcinoma (NSCLC) [23, 24] and chronic myeloid leukemia (CLL) [25]. The expression level of a certain miRNA has been used to determine whether the specific miRNA plays a tumor suppressive or oncogenic role in cancers [12]. If a miRNA was found to be highly expressed in cancer cells, the miRNA can be expected to play an oncogenic functions by targeting tumor suppressor genes. On the other hand, low expression level of a miRNA has been regarded as a tumor suppressor and those miRNAs are often found to target oncogenes. It has been reported that miR-138 is dysregulated across many cancer types [26]. According to the global transcriptome analysis on human cancer patient samples by The Cancer Genome Atlas (TCGA) Consortium, miR-138 has been found to express at low level in many types of human cancer [20]. Cumulating data obtained from cell line studies including HeLa, melanoma, breast, neuroblastoma and pancreatic tumor suggest that miR-138 may play a tumor suppressive role by targeting various oncogenes. An ectopic overexpression of miR-138 directly suppresses focal adhesion kinase (FAK), resulting in lowered invasiveness and increased susceptibility to chemotherapy [27]. Changes in miR-138 expression can affect cell proliferation, metastatic ability and drug resistance. Although this review will mainly focus on the tumor suppressive aspect of miR-138 in various human cancers, rare case of reports, however, will also be covered regarding an oncogenic role of miR-138 in malignant glioma patients [28, 29]. From these studies, putative targets of miR-138 is summarized in **Table 1**.

MiR-138 in brain tumor

In normal brain tissues, miR-138 is highly enriched within dendrites and regulates a depalmitoylation enzyme acyl protein thioesterase 1 (APT1) to control dendritic spine morphogenesis [30]. In mice study, the high level of miR-138 expression was correlated with better memory performance of the mice since miR-138 negatively inhibits APT1 expression [31]. The study speculated that increased APT1 expression occurs with aging due to the reduction of miR-138 level. In a similar vein, miR-138 expression

Table 1. Putative targets of miR-138 in human cancers

Cancer type	Function	Target
Glioblastoma (GBM)	Tumor suppressor	EZH2 [32]
		CDK6 [32]
		E2F2 [32]
		E2F3 [32]
		PD-1 [33]
		CTLA-4 [33]
	Oncogene	C/EBPβ [28]
		BIM [34]
Non-small cell lung cancer (NSCLC)	Tumor suppressor	EGFR [24]
		SIRT1 [36]
		GIT1 [77]
		SEMA4C [77]
		EZH2 [38]
		PDK1 [78]
		HOXA4 [24]
		SNHG12 [40]
Oral squamous cell carcinoma (OSCC)	Tumor suppressor	ISG15 [51]
		ΔNp63 [52]
		YAP1 [49]
		EZH2 [53]
		PD-1 [54]
		CTLA-4 [54]
Colorectal cancer (CRC)	Tumor suppressor	TERT [59]
		PD-L1 [58]
		PODXL [60]
		HMGA1 [61]
		TWIST2 [55]
		Lcn2 [57]
Renal cell cancer (RCC)	Tumor suppressor	EZH2 [69]
		FOXP4 [70]
Hepatocellular carcinoma (HCC)	Tumor suppressor	SOX9 [63]
		Cyclin D3 [62]
		Vimentin [65]
		CCND3 [65]
Prostate cancer	Tumor suppressor	EZH2 [44]
Cervical cancer	Tumor suppressor	SIRT1 [71,72]
Gastric cancer	Tumor suppressor	SOX4 [66]
		HIF-1α [67]

has been found to be reduced in brain tumors. Low expression levels of miR-138 were associated with progression-related poor survival of GBM patients according to the TCGA database [32]. The study also found EZH2, CDK6, E2F2 and E2F3 as the direct targets of miR-138, through which EZH2-CDK4/6-pRb-E2F1 signaling pathway was impaired by ectopic miR-138 expression. When human CD4+ T cells were transfected with miR-138, it was shown that the miR-138 can directly down-regulate two immune checkpoints, cytotoxic T-lymphocyte-associated molecule 4 (CTLA-4) and programmed cell death 1 (PD-1), and result in 43% increase in median survival time in mice models [33]. This study demonstrated a potential of miR-138 that can be translated into an immunotherapeutic agent.

In contrast, a few compelling reports have surfaced with a clue that miR-138 may act as an oncogenic miRNA. For examples, it was found that miR-138 was overexpressed in tumor-initiating glioma stem cell (GSC) [29]. Therefore, ectopic expression of miR-138 promoted self-renewal potential of GSCs resulting their growth and survival. They also found that the transcriptional activation of miR-138 in glioma is mediated by C/EBPβ [28]. In this regard, miR-138 was also found to promote acquired resistance to temozolomide (TMZ) by directly targeting an apoptosis regulator BIM [34].

MiR-138 in lung cancer

In primary lung cancer, miR-138 has been shown to be downregulated by pertinent exposure to TGFβ1 and result in increased stemness through epithelial mesenchymal transition (EMT) [35]. As the result, the population of CD44+CD90+ cancer stem cell (CSC) was increased. MiR-138 can also lower EMT properties through decreased activity of the AMPK signaling pathway by directly targeting SIRT1 [36]. ZEB2 was also found to be a direct target of miR-138 in lung adenocarcinoma, since the ectopic expression of miR-138 suppresses EMT, cell proliferation

and metastasis [37]. Overexpression of miR-138 suppressed cell proliferation by reducing expression of EGFR [24] or EZH2 [38]. In NSCLC, the transcription of miR-138 was regulated by direct binding of certain transcription factors, such as p53 [23] HOXA4 [24]. Interestingly, certain long non-coding RNAs (lncRNAs) also regulate the expression of miR-138 in lung cancer. For examples, PFAR plays as a competing endogenous RNA (ceRNA) of miR-138 in targeting regulation of yes-associated protein 1 (YAP1) leading to lung fibrosis [39]. In addition, small nucleolar RNA host gene 12 (SNHG12) was identified to be upregulated in NSCLC and negatively regulated miR-138 expression [40]. Overexpression of miR-138 also can sensitize lung cancer cell to conventional chemotherapeutic drugs. For an example, NSCLC patients used to develop acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) such as gefitinib. Ectopic expression of miR-138 in NSCLC cells restored gefitinib activity of cell killing by directly targeting G protein-coupled receptor 124 (GPR124) [41].

MiR-138 in prostate cancer

Comprehensive miRNA profiling study from 37 patients has identified miR-138 as one of the down-regulated miRNAs in prostate cancer [42]. Comparison of miRNA profile between normal stem cell and cancer stem cell in prostate cancer cells revealed the inverse correlation between miR-138 expression and KRAS [43]. Exogenous miR-138 expression in prostate cancer cells directly targeted EZH2 resulting in cell cycle arrest in the G1/G0 phase [44]. MiR-138 overexpression can also reduce tumor migratory ability through down-regulation of the Wnt/B-catenin pathway [45, 46].

MiR-138 in head and neck cancer

MiR-138 expression has been found to be down-regulated in many types of head and neck cancer patients. Two-step reverse transcriptase-quantitative PCR (qRT-PCR) using TaqMan miRNA Assays on 42 oral squamous cell carcinoma (OSCC) tumors and 8 adjacent normal specimens revealed that miR-138 is one of the most significantly down-regulated miRNAs together with miR-184 [47]. In contrast, another miRNA profiling study on 35 oral cavity and oropharynx squamous cell carcinoma (SCC) samples and 10 non-neoplastic oral mucosa controls also identified miR-138 as one of up-regulated miRNAs in 50% of samples [48]. This discrepancy needs to be resolved by examining more patient groups by their grade levels.

As observed in lung cancer, miR-138 suppresses cell proliferation through targeting YAP1 in OSCC [49]. In another study with OSCC cells, forced expression of miR-138 in OSCC cells significantly decreased promoted cell adhesion and inhibited migration, invasion and EMT by directly targeting fascin to reduce filopodia formation and paxillin expression [50]. The low expression level of miR-138 was also correspond with high expression of interferon-simulated gene 15 (ISG15) in OSCC [51]. In the study, over-expression of miR-138 in OSCC cells resulted in reduced ISG15 expression through direct binding to its 3' UTR causing inhibition of invasion, proliferation and migratory ability [51]. DeltaNp63 (ΔNp63), the predominant isoform of TP63, was found to be significantly up-regulated in OSCC tissues in the negative correlation with miR-138 expression. Direct targeting of ΔNp63 by miR-138 mitigated its overexpression in cancerous OSCC cells to reduce cell growth, metastasis and stemness [52]. LncRNA, H19, was found to be highly expressed in OSCC in an inverse correlation with miR-138 and play an oncogenic role by competing with miR-138 to bind to the 3' UTR of EZH2 mRNA [53].

Recently, there was an attempt to restore miR-138 in OSCC as a therapeutic purpose. Li and colleagues used gamma-delta T cell-derived extracellular vesicles (γδTDEs) as drug delivery system (DDS) for miR-138 [54]. Interestingly, miR-138 immunization via γδTDEs into OSCC bearing immunocompetent mice did not inhibited the tumor growth. However, injection of the miR-138 in γδTDE into immunocompetent mice increased immune response to OSCC tumor by increasing the proliferation, interferon-gamma (IFN-gamma) production and cytotoxicity of CD8+ T cells possibly through direct targeting of programmed cell death 1 (PD-1) and CTLA-4 of CD8+ T cells by the cargo miR-138 [54]. This finding is interesting since miR-138 showed its potential for immunotherapy.

MiR-138 in colorectal cancer

In colorectal cancer (CRC) tumors and cell lines, miR-138 is mostly found to be downregulated

[55, 56]. Its downregulation is linked to increased metastasis and poor prognosis through up-regulation of Twist basic helix-loop-helix transcription factor 2 gene (TWIST2) [55], which is a target for miR-138. In a metastasis to livers, miR-138 was also shown to target lipocalin 2 (Lcn-2) in a relationship to increased lipid metabolism [57]. As in brain tumor, miR-138 was shown in CRC to target an immunocheck point PD-L1 [58, 59]. Xu and colleagues reported that Podocalyxin-like (PODXL) plays an oncogenic role in the development and progression of CRC and miR-138 directly targets PODXL as a tumor suppressor [60]. LncRNA was also found to correlate with miR-138 in CRC. For an example, lncRNA H19, which is highly overexpressed in CRC, was inversely correlated with miR-138 in CRC and its downstream target high-mobility group A (HMGA1) was shown to be directly targeted by miR-138 [61]. For these observations, it was proposed that inhibition of oncogenic miR-21 and induction of tumor suppressive miR-138 will be beneficial in CRC treatment [56].

MiR-138 in liver cancer

In hepatocellular carcinoma (HCC), more than 70% of the HCC patients showed the down-regulated level of miR-138 expression [62]. It was shown that miR-138 inhibits cell proliferation and invasion by directly targeting SOX9 or cyclin D3, therefore ectopic expression of miR-138 in HCC cells was expected to function as a useful therapeutics [62, 63]. In another study, down-regulated expression of miR-138 was found to be inversely correlated with a putative oncogenic LncRNA DBH-AS1 [64]. Interestingly, they found that DBH-AS1 functions as a molecular sponge against miR-138 resulting in attenuated miR-138-mediated tumor suppressive roles through the rescue of FAK/Src/ERK pathway from miR-138. Similarly, circular RNA (circRNA) circRBM23 was found to overexpress in HCC patients in an inverse correlation with miR-138 expression [65]. In the study, miR-138 was down-regulated by circRBM23 resulting overexpression of oncogenic proteins, such as vimentin and CCND3.

MiR-138 in other cancers

In other cancers, miR-138 was also mostly found to be down-regulated to function as a tumor suppressor. In gastric cancer, miR-138 is consistently down-regulated in tumor tissue and cell lines [66]. The study found that the low level of miR-138 expression corresponds with increased EMT from both tumor node and lymph nodes through its direct target SRY-related high mobility group box 4 (SOX4), a master mediator of EMT. LncRNA LINC00152 was found to overexpress in gastric cancer and functions as a molecular sponge for miR-138 to rescue hypoxia inducible factor-1α (HIF-1α) suppression [67]. CREPT regulates oncogenic beta-catenin/TCF4/cyclin D1 pathway in breast cancer, and is directly targeted miR-138 that is found to be down-regulated in most breast cancer patients [68]. MiR-138 is also down-regulated in renal cell carcinoma (RCC) and found to induce cell senescence by targeting EZH2 [69]. Interestingly, estrogen receptor β (ER-β) induces an oncogenic lncRNA, HOTAIR, in RCC, which antagonizes tumor suppressive miRNAs including miR-138 [26]. Recently, circRNA ZNF609, which was found to overexpress in RCC, was also shown to compete with miR-138 to target forkhead box P4 (FOXP4) [70]. In cervical cancer, SIRT1 was shown to be targeted by miR-138 which, in turn, can be sponged by up-regulated lncRNA TUG1 or H19 [71, 72].

Perspectives

Discovery of miRNAs has highlighted their profound functions in almost every cellular pathways human cancers during cancer initiation, progression, migration and metastasis. Global miRNA profiling from a number of patient cohorts in various type of human cancers has identified miR-138 as a signature of tumor suppressor that are mostly down-regulated in cancer cells. Only in rare cases, miR-138 was found to be up-regulated, such as in cancer stem cells. As a tumor suppressor, miR-138 can inhibit oncogenic proteins by directly binding to their mRNAs. More importantly, accumulating evidence has shown that miR-138, as other miRNAs, can regulate multiple targets in cancer cells. These findings make miR-138 as an attractive therapeutic option to treat human cancers. Interestingly, it was observed only in brain tumors that miR-138 can function as an oncogenic miR in certain type of brain tumor cells. Although these controversial results regarding the functional role of miR-138 in brain tumors need to be further resolved, it may imply the possibility of dual functional role

of miRNAs depending on the context. The most studies about down regulation and corresponding tumor suppressive function of miR-138 were obtained from primary brain tumors. However, the oncogenic role of miR-138 was observed in either GSCs or chemotherapy-resistant cells. It will be interesting to test whether the recurring brain tumor cells are related to the overexpression of miR-138 and how miR-138 changes its functions and targets depending on cell context not only in brain tumor also in other types of cancer. In order to use miR-138 for translational purpose of clinical therapeutics, it will be a critical issue to decide whose patients need to be treated with miR-138 overexpression or miR-138 inhibitors. Therefore, future studies will need to focus on how to deliver such therapeutically potent miR-138 into a specific cancer cell type to inhibit cancer progression and metastasis. Although many of such attempts to delivery miRNAs into cancer cells have not been successful, emerging new strategy for cell and tissue specific delivery are promising to accomplish this task. Our recent progress on RNA nanotechnology may solve these hard issues. We have shown that RNA-based nanoparticle or exosomes can successfully provide efficient and safe targeted delivery method for such small noncoding RNAs including siRNAs and miRNAs [73-76]. Nevertheless, miRNA-based cancer therapy needs further understanding in detail for their functional mechanism through target down-regulations in order to surpass or complement conventional treatment options to improve patient outcome.

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Disclosure of conflict of interest

None.

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