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Effect of miRNAs in lung cancer suppression and oncogenesis

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Abstract: MicroRNA (miRNAs) is a group of small non-coding RNAs. It is involved in multiple cellular processes including proliferation, development, metabolism, differentiation and apoptosis; many of which are linked to several pathological conditions, including cancer. Lung cancer is one of the leading causes of mortality in the world: in 2008 for example, there were 163,000 deaths as a result of lung cancer. Despite technologies emerging which provide the potential for novel targeted therapies and improved early diagnoses, the overall rate of five-year survival still remains at only 15%. One reason for this disappointing statistic is related to the presentation of the disease, and specifically a lack of markers for early detection. Notably, the expression of some miRNAs has been reported to be involved in the diagnosis, classification and even prognosis of lung cancer. Tumor-suppressive and oncogenic miRNAs were found in lung carcinogenesis and the biological functions of these miRNAs have been validated in transplantable lung cancer models and human paired normal-malignant lung tissue banks. Some of these tumor-suppressive and oncogenic miRNAs related to lung cancer will be reviewed here. This article will focus on emphasizing miRNAs effectiveness as a biomarker in lung carcinogenesis and candidate pharmacology. Furthermore, how these findings improve our understanding of lung cancer biology and therapy will also be discussed.

Keywords: miRNA, lung cancer, suppression and oncogenesis.

1 Introduction

Lung cancer results in more deaths than any other cancer, including breast, colon and prostate tumors. According to clinic pathology, lung cancer is divided into two categories: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), with NSCLC being more common around the world.

miRNAs have been identified to be closely related to cancer research and as of 2015, there were over 2500 miRNAs described in the human genome miRBase [1]. Generally, the function of miRNAs in cancer has been divided into two categories: oncogenic or tumor suppressor miRNAs. The miRNAs with oncogenic functions inhibit mRNA during post-transcription and then lower the protein levels of molecules with tumor suppressor functions. Conversely, miRNAs with tumor suppressors may also target DNA methyltransferases (DNMT) 3A and 3B except for mRNA and protein [2]. Meanwhile, cell and tissue context as well as the physiological and pathophysiological states have a substantial influence on gene expression when miRNA-mediated. For cancer production and development, uncontrolled cell proliferation is undoubtedly an essential step and during this process aberrant miRNAs expression has a great influence on tumor cell growth [3]. This article will discuss how miRNAs acts as a mediator in lung cancer suppression and oncogenesis.

2 Oncogenesis miRNAs in lung cancer

When compared to adjacent normal lung tissue, oncogenic miRNAs are defined by a higher expression of miRNAs in the malignant lung tissues. Takahashi ^[4] found that the miRNA-17~92 cluster specifically is markedly overexpressed in lung cancer cells and is related to enhanced cell growth [4]. miRNA profiling studies [5] have also revealed which members are overexpressed in this cluster. When miR-17-5 p and miR-20a are inhibited along

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with antisense oligonucleotides, miRNA-17~92 – which is overexpressed in lung cancer – will induce selective apoptosis. This suggests an oncogenic function of miRNA-17~92 [6]. Transactivation by *E2F* family members [7] and *MYC* [8] also has a close relationship with miRNA-17 ~ 92 expressions. *MYC* is generally overexpressed in SCLC [9] and *HIF-1 α* – as one of direct targets of miRNA-17~92 – is downregulated by *MYC* [10]. This relationship further suggests that miRNA-17~92 affects cell proliferation of lung cancer. SBC-3, a SCLC cell line, has been examined using the proteomic approach to identify other targets of miRNA-17~92, one of which is the RAS-related protein 14 (*RAB14*), which induces surfactant secretion in the lungs [11]. A related study showed that miRNA-17~92 could induce *RAB14* downregulation, which may could therefore lead to lung tissue that is sensitive to external carcinogens [11].

Some oncogenic miRNAs are identified as potential prognostic biomarkers and these include miR-92a-2 in SCLC [12] and miR-155, miR-30e-3p, miR-130a and let-7f in NSCLC [13-15]. Among oncogenic miRNAs, miR-21 is especially noteworthy, as Zhu et al. illustrated that it may induce the downregulation of specific sets of target genes to facilitate tumor invasion and metastasis [16]. This process involves the expression products of pro-apoptotic genes such as Apaf1, Faslg, Pdcd4 and RhoB [17,18].

Another promising anti-tumor target is the Apo2L/TNF- α -related apoptosis-inducing ligand (*TRAIL*), which is a member of the recently identified TNF family [19]. It is reported that when miR-221/222 was upregulated in NSCLC, *TRAIL* was resisted [19]. Two genes *Kit* and *p27Kip1* are related to this kind of regulation and a study has revealed that a decrease in the level of *p27Kip1* seems to explain a decreased sensitivity to *TRAIL*-related apoptosis [20].

It is reported that miR-494 is upregulated when human bronchial epithelial cells are transformed by a chemical carcinogen [21], suggesting that miR-494 acts as an oncogenic miRNA by inhibiting apoptosis of cancer cells. Meanwhile, miR-328 is generally overexpressed in lung tumor patients with brain metastases due to it promoting cell migration [22]. Inhibition of miR-301 hosted in the SKA2 gene could induce an increase of cell proliferation and invasion through the *ERK/CREB* pathway by promoting colony formation and the mitotic index [23]. miR-93, miR-98 and miR-197 could directly downregulate *FUSI* gene with tumor suppressive activity, which promotes lung cancer growth [24]. Furthermore, miR-106 and miR-150 influence the regulation in lung cancer cell growth and apoptosis by targeting RB and *TP53* respectively [25].

2.1 Tumor suppressive miRNAs in lung cancer

Contrary to oncogenic miRNAs, tumor suppressive miRNAs are normally suppressed in lung cancer. For example, of the earliest known miRNAs, let-7, shows suppression in bronchioloalveolar carcinoma [26] and lung adenocarcinoma [27,28]. As members of the let-7 family, let-7a-1, 7a-2, 7a-3, 7b, 7c, 7d, 7e, 7f-1, 7f-2, 7g, 7i, miR-98 and miR-202 were subsequently uncovered in *C. elegans* [29,30]. The miR-34/449 family however were found to control apoptosis and cell cycle arrest in lung cancer cell lines by directly regulating transcription factors *p53* and *E2F* [31,32]. As an example, inactivated miR-34a may cause transcription silence in lung cancer through CpG methylation, which indicates that miR-34a may be used as a biomarker for NSCLC [33,34]. Based on these directly targeted genes, miRNAs of miR-34/49 are categorized into four classes: (a) targeting *CDK4/6*, *c-MYC*, *E2Fs*, *CCNE2* and *MET* for arresting cell cycle; (b) targeting *c-MYC*, *SIRT1* and *HDMX* for activating senescence; (c) targeting *BCL-2*, *N-MYC*, *HDAC1* and *MET* for rendering apoptosis; and (d) targeting *SERPINE1*, *AXL*, *SNAIL1* and *HMG2* [35-38].

miR-15a and miR-16-1 together with miR-15b and miR-16-2 belong to the cluster of miR-15/16, and when the deletion or downregulation of miR-15 and miR-16 occurs, many phases of lung cancer development – including proliferation, invasion and cell survival – are inhibited [39]. This phenomenon suggests their role as tumor suppressors. The regulation progression however does involve many genes, including *BCL-2*, *CCND1*, *ETS1*, *JUN*, *MSH2* and *WNT3A* [40].

Located at chromosome 1 and chromosome 12, miR-200 acts as an inhibitor in epithelial-mesenchymal transition (EMT) by targeting *ZEB1* and *ZEB2* [41]. This highlights the role of miR-200 in the regulation of cancer pathogenesis by facilitating the invasion and metastasis of lung cancers. Previous work has revealed that upregulation of miR-200 in lung tumor cells prevents cancer cells going through EMT, thus weakening the potential for cellular invasion and metastasis [42]. miR-205 is another suppressor miRNA that has the same mechanism as miR-200 [43]. A recent study suggests that miR-205 together with miR-200 downregulate GATA3, which is a component of Notch signaling in promoting metastatic colonization to the lung [44] and sensitivity of lung cancer cells to multidrug [45].

In humans, miR-143 and miR-145 are located on chromosome 5 [46]. Previous work has shown that miR-143 and miR-145 expression levels are downregulated in rodent lungs exposed to cigarette smoke (which is a severe carcinogen) [46]. Additional studies have shown

that miR-143 and miR-145 have an inhibitory effect on lung cancer cell growth in both mice and humans [47]. This regulation progress involves many target genes, such as *C-MYC*, *NUDT1*, *EGFR* and *OCT4* [48].

miR-29 plays an indirect role in the inhibition of tumorigenicity through demethylation by DNA methyltransferases *DNMT3A* and *-3B* [49]. miR-126 has also been identified as an important inhibitory factor of vascular proliferation via the suppression of vascular epithelial growth factor (VEGF) [50]. Therefore miR-126 is identified as a tumor suppressor because it will be downregulated in cases of lung cancer [51].

There are three miRNAs, miR-1, miR-133 and miR-206, which are highly expressed in cardiac and smooth muscle tissues and, have been found to exhibit cancer suppressive activities [52]. miR-1 appears to have some role in the inhibition of cell growth, tumorigenicity and clonogenic survival when it is downregulated [53]. This likely involves many target genes, including *MET*, *PIM-1* and *FOXPI*. miR-133a meanwhile has higher levels of expression in lung squamous cell carcinomas [54]. The expression of miR-206 is lower in metastatic tumors and thus when it is inhibited, cell proliferation, invasion and migration may be motivated [55].

2.2 Some miRNAs that show both oncogenic and suppression actions on lung cancer

In different contexts, individual miRNAs may show both oncogenic and suppressive actions in lung cancer.

miR-31, located on chromosome 9, can be induced by carcinogens in lung tissue [56] and has been shown to acts as an oncogenic in mouse and human lung cancer [57]. After potential target genes were uncovered via bioinformatic analysis, two tumor suppressor genes were found: *LAST2* and *PPP2R2A* [58]. Further, when targeting *ITGA5*, *RDX* and *RhoA*, miR-31 may induce the recession of cancer cell metastasis and show suppressive tendencies [59].

In 2008, miR-7 was identified as a suppressive miRNA in tumors [60]. miR-7 acts in this suppressor role by targeting *EGFR* and *BCL-2*, along with downregulation of the AKT pathway which inhibits the viability and growth of cancer cells [61]. On the contrary however, targeting *EGFR* as well as *PAS/ERK/MYC* pathway induces miR-7 expression, which promotes proliferation and tumorigenicity [62].

miR-125 has two different members, miR-125a and miR-125b. In 2007, the miR-125 family was identified as a tumor suppressor via the downregulation of the *ERBB2*

and *ERBB3* genes [63]. On the other hand, miR-125a/b also show oncogenic behavior due to the targeting of *TP53* [64].

3 Future directions of miRNAs of lung cancer

The study of miRNAs is a promising method to improve the accuracy of diagnosis, classification and clinical prognostic information for lung cancer cases. However, it is necessary to match the miRNA feature to the corresponding subtype of lung cancer. For targeted therapies, miRNA profiles may help to predict patient response. Even for people not suffering from lung cancer, miRNA profiles might identify those individuals with a higher risk of developing of lung cancer, which may then enable them to alter their lifestyle.

Currently, in order to analyze the necessary miRNA expression, genetically-engineered mouse models of lung cancer have been established which simulate patients. Accordingly, when a miRNA is identified as a candidate for tumor suppression or oncogenesis, its function will be confirmed by gain/loss studies of miRNA in the established model [65]. Then, when a specific miRNA is found to play an important role in lung cancer development, specific targeting to reduce lung carcinogenesis within the same species will be attempted. Generally, chemically-modified RNA analogs are remarkable therapeutic agents. These RNA analogs have the advantage that they minimize off-target toxicity and so far been well tolerated in clinical studies [65]. Of course, there are possible disadvantages to this too, in is that the deregulation of a single targeted miRNA may induce global changes in gene expression, which may lead to adverse effects or even toxicity.

4 Conclusion

As the most common cause of cancer mortality, the development of lung cancer is closely tied to miRNAs. It is therefore necessary to harness the full knowledge so far uncovered about the role of miRNAs in regulating gene expression in lung cancer. The primary challenge for miRNA therapy however is improving the control of delivery; especially in relation to therapy stability and off-target effects. Nonetheless, further improvements in the treatment of lung cancer are undoubtedly urgent. Current studies will give us information as to whether miRNA strategies could be used alone or in combination with chemotherapy to improve the specificity and efficacy of current treatments.

Abbreviations

AKT v-akt murine thymoma viral oncogene homolog
AXL AXL receptor tyrosine kinase
BCL-2 B-cell CLL/lymphoma 2
CCND1 cyclin D1
CCNE2 cyclin E2
CDK4 cyclin-dependent kinase 4
CDK6 cyclin-dependent kinase 6
c-MYC v-myc myelocytomatosis viral oncogene homolog
E2F E2F transcription factor 1
EGFR epidermal growth factor receptor
ERBB2/3 v-erb-b2 erythroblastic leukemia viral oncogene homolog 2/3
ETS1 v-ets erythroblastosis virus E26 oncogene homolog 1
FUS1 fused in sarcoma
HDMX Mdm2 p53 binding protein homolog
HIF-1 α hypoxia inducible factor 1, alpha subunit
HMGA2 high mobility group AT-hook 2
ITGA5 integrin, alpha 5
MET met proto-oncogene
MSH2 mutS homolog 2
NUDT1 nudix (nucleoside diphosphate linked moiety X)-type motif 1
OCT4 POU class 5 homeobox 1
PPP2R2A protein phosphatase 2 regulatory subunit B alpha
SERPINE1 serpin peptidase inhibitor clade E
SIRT1 sirtuin 1
SNAIL1 snail homolog 1
TP53 p53 tumor suppressor
WNT3A wingless-type
Conflict of interest: Authors declare nothing to disclose.

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