Association of miR-210 and Lung

Subjects: Allergy
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MicroRNA is a class of non-coding RNA involved in post-transcriptional gene regulation. Aberrant expression of miRNAs is well-documented in molecular cancer biology. Extensive research has shown that miR-210 is implicated in the progression of multiple cancers including that of the lung, bladder, colon, and renal cell carcinoma. In recent years, exosomes have been evidenced to facilitate cell–cell communication and signaling through packaging and transporting active biomolecules such as miRNAs and thereby modify the cellular microenvironment favorable for lung cancers. MiRNAs encapsulated inside the lipid bilayer of exosomes are stabilized and transmitted to target cells to exert alterations in the epigenetic landscape.

Keywords: micro-RNA ; miR-210 ; exosomes ; lung cancer

1. Introduction

Over the past few decades, tremendous strides have been made in understanding the genetics and treatment of lung cancer. However, lung cancer remains the prevailing cause for global cancer-related morbidity and mortality [1]. Lung cancer is classified into two histological subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [2]. NSCLC, which includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, is the most prevalent, covering approximately 80% of all lung cancer cases [3]. SCLC is less commonly found (15–20%) but is known to proliferate and metastasize more rapidly than NSCLC. In addition to these two main types, rare lung tumors such as carcinoid tumors, adenoid cystic carcinomas, sarcomas, and benign hamartomas have also been reported. Despite a wide array of currently available treatment methods including surgery, radiotherapy, chemotherapy, and immunotherapy, the 5-year survival rate of lung cancer patients is still under 20% [4]. Poor disease prognosis is in part due to limited understanding of the complex nature of lung tumor heterogeneity as well as late disease presentation and diagnosis. Notably, cancers are known to have long incubation periods (~20 years), during which time, the sensitivity of typical detection methods such as ultrasound, x-ray-based computer tomography, and endoscopy are inept. In recent years, liquid biopsy has become a widely used technique in clinical settings due to its ease of use, minimal invasiveness, and low cost. Most important, genomic information, such as global gene expression dysregulation, extracted from biofluids provide higher accuracy for disease detection as well as insights for underlying mechanisms of disease pathogenesis.

Aberrant expression of microRNAs (miRNAs) has been well-documented in lung cancer. Elevated oncogenic or reduced tumor suppressive miRNAs are equally important in altering cancer-related signaling pathways, and have been implicated in tumor cell growth, angiogenesis, and metastasis. In body fluids, miRNAs exist as circulating Ago protein-bound forms that are either released from damaged and dead cells or selectively packaged into extracellular vesicles (EVs) for cell signaling purposes [5][6][7]. Exosomes have been evidenced to play an important role in mediating cell–cell communication through transferring and depositing active biomolecules such as miRNAs, thereby eliciting epigenetic changes in recipient cells. Various exosomal miRNAs are dysregulated in lung cancer. In particular, miR-21, miR-31, and miR-192 are most commonly found in human lung cancer tissues and blood samples [8][9][10][11]. Through a comprehensive literature search, we find that aberrant expression of exosomal miR-210 is found across various human, cell, and animal models of lung cancer, indicating an important role in cancer development. MiR-210 is a peculiar miRNA; apart from various cancers, its dysregulation is also associated with other human diseases such as cardiovascular disease and diabetic obesity [12][13]. What is more interesting is that its inclusion in exosomes in response to hypoxia is also relevant in placental disorder preeclampsia [14].

2. Mechanisms of Exosomal miR-210 in Lung Cancer

In 2009, Rabinowits et al. first reported that miRNAs extracted from NSCLC tissue can serve as diagnostic biomarkers [15] [16]. Since then, various miRNAs have been implicated in the development of lung cancer, and miR-21 has been one of the most extensively studied candidates. However, while dysregulation of exosomal miR-210 has been reported in human,

cell, and animal studies (**Table 1**), less is known about its underlying mechanisms in lung cancer. This section will examine all currently known mechanistic pathways involved in exosomal miR-210-mediated lung cancer.

Table 1. MiR-210 expression in human, cell, and mouse models.

Exosomal miRNA	miR-210	miR-210-3p	miR-210-3p	miR-210-3p	miR-210	miR-210
Expression Level	Up	Up	Up	Up	Up	Up
Sample Source	Human	Cell	Cell	Cell	Cell	Fox Chase SCID mice
Sample Type	Pleural effusion	HCC827 cells, PC-9 cells, HCC827-OR cells, PC-9-OR cells	H358 cells, A549 cells, H460 cells	A549 cells, NCIH1703 cells, BEAS-2B cells	A549 cells, HEK-293/EBNA cells	Plasma
Exosome Isolation Method	Exosome isolation reagents (Invitrogen)	differential centrifugation	EXO Quick	ultracentrifugation	ExoQuick-TC	ExoQuick-TC
miRNA Detection Method	qRT-PCR	miRNA microarray and qRT-PCR	miRNA microarray	qRT-PCR	qRT-PCR	qRT-PCR
Upstream Regulator	unknown	unknown	unknown	unknown	TIMP-1	TIMP-1
Downstream Target	unknown	unknown	STAT3 signalling	FGFRL1	EphA3	FGFRL1, E2F3, VMP-1, RAD52 and SDHD
Function	unknown	Drug resistance	Invasion, Metastasis, EMT	pro-proliferative	Angiogenesis	Vascularization
Cancer Type	adenocarcinoma	NSCLC	NSCLC	Not specified	adenocarcinoma	adenocarcinoma
Reference	[9]	[17]	[18]	[19]	[20]	[21]

2.1. Signal Transducer and Activator of Transcription 3 (STAT3)

Hypoxic bone marrow-derived mesenchymal stem cells (BMSCs) have been evidenced to transfer exosomal miRNAs to promote lung cancer metastasis. Specifically, lung cancer cells (A549, LLC, H460, and H358) treated with hypoxic BMSC-derived exosomes demonstrated increased migration and invasion potentials compared to normoxic BMSC-secreted exosomes [18]. Hypoxic BMSC-derived exosomes were especially rich in miR-193a-3p, miR-210-3p, and miR-5100. Furthermore, BMSC-derived exosomes promoted both the total and phosphorylated STAT3 levels [18]. STAT3 is known to be overexpressed in cancer cells, and functions to elicit production of immunosuppressive factors. Moreover, miR-210-3p inhibitor was capable of reducing phosphorylated STAT3 expression. The study further analyzed plasma exosomes and found significantly upregulated miR-210-3p levels in metastatic lung cancer patients compared to non-metastatic lung cancer patients and healthy controls, suggesting that miR-210 may play an important role in lung metastasis. Specifically, miR-210-3p is capable of targeting STAT3 inhibitor, suppressor of cytokine signaling 1 (SOCS1) [22]. Interestingly, miR-210-5p has also been shown to directly target SOCS1 in RCC [23].

2.2. Fibroblast Growth Factor Receptor Like 1 (FGFRL1)

Cancer cells have high heterogeneity and contain a variety of cell types. Cancer stem cells (CSCs) for example, make up a small population of cancer cells, and are characterized by enhanced self-renewal and chemo/radiotherapy resistance capabilities, which make them the main mediators for sustained cancer growth. Lung CSC-derived exosomes have been evidenced to contain high levels of miR-210-3p and enhance lung cancer cell migration and invasion, through the inhibition of E-cadherin as well as the promotion of vimentin, N-cadherin, MMP-9, and MMP-1 expression, which are phenotypic hallmarks for EMT and enhanced invasive potential [19]. Moreover, the study indicated that miR-210-3p may contribute to cancer cell metastasis via the inhibition of FGFRL1. FGFRL1 is part of the FGFR family and has been

reported to modulate ERK1/2 and FGF signaling pathways [24]. Recently, FGFRL1 has been associated with prostate, gastric, oesophageal, and ovarian cancer cell proliferation and metastasis [25][26]. In particular, miR-210 has been evidenced to promote angiogenesis by targeting FGFRL1 in hepatocellular carcinoma and osteosarcoma cells [27][28]. However, in oesophageal squamous cell carcinoma, laryngocarcinoma, and bladder cancer, miR-210-3p has showed tumor suppressive properties through FGFRL1 binding [29][27][30]. These conflicting results suggest that miR-210-3p and FGFRL1 may have dual roles in cancer.

2.3. PI3K/AKT Pathway

Runt-related transcription factor-3 (RUNX3) is primarily involved in cartilage mineralization and chondrocyte maturation, though evidence suggests that miRNA-regulated RUNX3 is capable of influencing phosphatidylinositol-3-kinase protein kinase B (PI3K/AKT) signaling pathway, which is crucial for cancer cell proliferation [31][32][33]. RUNX3 is correlated with poor prognosis and shorter survival in NSCLC patients [34][35]. A study led by Li et al. reported that miR-210 was capable of inhibiting RUNX3, thereby activating PI3K/AKT signaling pathway and promoting malignant phenotype of lung cancer cells [35]. Conversely, the inhibition of miR-210 or PI3K/AKT signaling pathway via LY294002 treatment reversed malignant potential of lung cancer cells. In addition to RUNX3, PTEN is another well-known regulator of the PI3K/AKT signaling pathway. For example, overexpression of miR-210 has been shown to promote NSCLC cell migration and invasion through UPF1 suppression followed by upregulation of the PTEN/PI3K/AKT pathway [36]. More recently, miR-210 upregulation has been reported to inhibit upstream stimulating factor 1 (USF-1) and polycomb group ring (PCGF3) [37]. USF-1 is a transcription factor belonging to the basic helix-loop-helix leucine zipper family, and is known to regulate hepatocellular carcinoma, papillary thyroid as well as lung cancer [38]. Interestingly, PCGF3 has also been reported to promote cell proliferation in NSCLC via the PI3K/AKT signaling pathway [39]. Moreover, miR-210-mediated PI3K/AKT signaling has also been reported in oral cancer. Notably, in oral squamous cell carcinoma, elevated exosomal miR-210-3p levels can inhibit ephrinA3 expression and in turn activate PI3K/AKT signaling pathway [40]. Overall, these studies suggest that miR-210 can alter PI3K/AKT through various factors, and that this phenomenon is not limited to lung cancer.

2.4. Tissue Inhibitor of Metalloproteinases-1 (TIMP-1)

TIMP-1 is known to regulate protease homeostasis via the inhibition of metzincin [41][42]. Its ability to inhibit matrix metalloproteinases (MMPs) and A-disintegrin-and-metalloproteinase (ADAM-10) reflect anti-tumorigenic characteristics. However, increased TIMP-1 expression is often correlated with poor prognosis, especially in ovarian, lung, gastric, and papillary thyroid carcinoma [43][44][45][46][47][48]. Interestingly, TIMP-1 serves as a positive regulator of PI3Ks and has been evidenced to promote cancer cell growth via AKT/ERK phosphorylation [49][50][51][52][53]. A study led by Cui et al. showed that an increase in TIMP-1 promoted lung cancer progression through activating the PI3K/AKT/HIF-1 signaling pathway and miR-210 expression [21]. Specifically, high levels of miR-210 were found in exosomes derived from TIMP-1 overexpressing A549L cells, and that its expression level was dependent on HIF-1 accumulation. Conversely, a reduction in miR-210 can effectively inhibit A549L cell growth, suggesting its important role in cancer cell proliferation. Previous research has reported that hypoxia promotes exosome secretion of miR-210, suggesting a mechanism of a self-sustaining hypoxia state. Moreover, the study finds that levels of mature miR-210 was dependent on CD63, an interacting partner of TIMP-1, providing novel insight into the mechanism of elevated miR-210 in lung cancer.

2.5. Epidermal Growth Factor Receptor (EGFR)-Mutant Drug Resistance

Osimertinib is a tyrosine kinase inhibitor, specifically designed to treat EGFR-mutant non-small cell lung cancer [54][55]. Despite its effectiveness compared to previous two generations of EGFR-tyrosine kinase inhibitors (EGFR-TKIs), multiple studies have reported resistance to osimertinib, due to varying mechanisms, including EGFR mutation, KRAS mutation, BRAF mutation, loss of T900M mutation, or HER2 amplification [56]. Using microarray and qRT-PCR, Hisakane et al. reported high levels of exosomal miR-210 in osimertinib-resistant HCC827-OR and PC-9-OR cells compared to HCC827 and PC-9 parental cells [17]. Moreover, co-culturing exosomes isolated from osimertinib-resistant cells as well as induction of miR-210 both led to drug resistance and EMT in oximertinib-sensitive cells. However, there was no evidence that miR-210 acted via the EGFR signaling pathway, suggesting the involvement of a bypass mechanism. The study points to E-cadherin as a potential mediating factor associated with EMT. In addition, exosomes isolated from colorectal cancer cells and pancreatic cancer stem cells have also been found to carry high abundance of miR-210 and are correlated with fluorouacil and gemcitabine resistance [57][58][59].

2.6. KRAS BACH2/GATA-3/RIP-3

Mutant KRAS is a well-known driver of lung neoplasia, part of which functions through secreting exosomes to manipulate tumor microenvironment favorable for hypoxic immunosuppression [60][61][62]. Interestingly, in KRAS chemoresistant lung

cancer tissues from human patients, high abundance of miR-146 and miR-210 were found compared to non-KRAS metastatic samples [62]. Moreover, post KRAS exosome inhibition, miR-210 expression levels were reduced, suggesting a direct relationship between KRAS and miR-210 levels. In addition, levels of miR-146/miR-210 were found at lower levels in lymph node metastatic tissues, indicating their importance in primary lung tumor. The study went on to report that KRAS was capable of regulating chromatin remodeling genes SMARCE1/NCOR1, which play key roles in chemosresistant metastasis, as well as transcription factor BACH2/GATA-3 expression through pyruvate/PKM2-dependent metabolism, thereby contributing to sustained immunosuppressive metastasis [62]. Although the mechanism of how miR-210 is regulated by KRAS remains elusive, there is clear evidence that PKM2 is an HIF-1 target gene [63].

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