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Review

Long noncoding RNAs in respiratory diseases

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Summary. Recently developed RNA microarrays and high-throughput sequencing techniques have demonstrated that long non-coding RNAs (lncRNAs) play important roles in a wide range of biological processes. Emerging evidence has confirmed the relevance of lncRNAs to diverse types of human disease, including cancer and cardiovascular disease. In this review, we discuss the important functions of lncRNAs in respiratory diseases. Because the reviewed studies have mainly focused on non-small cell lung cancer, future work will need to extend the studies into other respiratory diseases. From a clinical perspective, targeting lncRNAs as a novel therapeutic strategy in respiratory diseases will require further study to further clarify their biological functions.

Key words: MALAT1, HOTAIR, H19, MEG3, GAS5, Lung cancer, Asthma, Pulmonary fibrosis

Introduction

The central dogma of molecular biology posits that genetic information normally flows from DNA to RNA to protein. Although most of the genome is transcribed into RNA, the protein-coding genes account for only 1.5-2% of the genome (Alexander et al., 2010). Most of the human genome encodes RNAs that do not code for proteins. Although these non coding (nc) RNA transcripts lack the potential to encode proteins, they have been shown to have important roles in various biological processes. NcRNAs are divided into two subclasses according to the transcript size: small ncRNA and long ncRNA. MicroRNAs are endogenous 19-24 nucleotide RNAs whose primary function is to restrain protein production by binding to target mRNAs in a sequence-specific manner. In contrast, lncRNAs are commonly defined as those longer than 200 nucleotides. According to the relative location with the protein-coding gene, lncRNA can be divided into the following categories: exonic lncRNAs (antisense/sense), intronic lncRNAs (antisense/sense), overlapping lncRNAs (antisense/sense), and intergenic lncRNAs (lincRNAs) (Sang et al., 2015). LncRNAs have broad and wide-ranging regulatory functions at the epigenetic, transcriptional and post transcriptional levels (Kung et al., 2013).

LncRNAs have been found in both the nucleus and cytoplasm. The majority of the lncRNAs are located in the nucleus (Derrien et al., 2012). The molecular mechanisms for most lncRNAs remain largely unknown. The key gene-regulating mechanisms for lncRNA can be summarized as follows. 1) LncRNA can act as a modular scaffold to control protein complex formation and localization. For example, within the nucleus, lncRNA scaffolds influence the genome-wide binding sites and activity of mediator complexes such as polycomb repressive complex 1 (PRC1) (Bonasio et al., 2014) and polycomb repressive complex 2 (PRC2) (Rinn et al., 2007); transcription factors such as CREB (Yao et al., 2016) and SRF (Han et al., 2015); and RNA polymerase II (Batista and Chang, 2013). In the cytoplasm, lncRNA scaffolds have been demonstrated to impact gene expression by regulating the stability, degradation,

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translational activation, and translational repression of the mRNA (Briggs et al., 2015). 2) LncRNA molecules can influence gene regulation by acting as decoys that can sequester protein and RNA by binding to them and diverting them from their normal sites. For instance, Chen and Carmichael (2009) reported that the lncRNA NEAT1 (nuclear-enriched abundant transcript 1) regulates nuclear and cytoplasmic trafficking of specific mRNAs by sequestering them in nuclear paraspeckles and releasing them for translation when NEAT1 is downregulated. 3) LncRNAs that have intrinsic catalytic activities can serve as signaling molecules that can regulate gene expression in a temporal and spatial manner. For example, the lncRNA CCND1 allosterically modifies specific proteins to regulate their natural functions (Wang et al., 2008). 4) LncRNA can act as guide lncRNA to recruit chromatin-modifying enzymes to target genes via cis (proximal to the lncRNA locus) or trans (distal to the lncRNA locus) regulatory mechanisms (Modarresi et al., 2012; Vance et al., 2014). Here, we focus on the emerging roles of lncRNA in lung diseases.

LncRNA in lung cancer

Lung cancer can be divided into either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC), according to its histology. SCLC makes up 15% of lung cancer and is derived from Kulchitsky cells (Puglisi et al., 2010). NSCLC comprises adenocarcinoma, squamous, and large cell carcinomas. NSCLC accounts for up to 80% of lung cancer. Lung cancer is the leading cause of cancer-associated mortality among males in both more and less economically developed countries and has surpassed breast cancer as the leading cause of cancer death among females in developed countries (Torre et al., 2015). Every year, 1.8 million people are diagnosed with lung cancer, and 1.6 million people die as a result of the disease. The 5-year survival rates vary from 4-17% depending on the stage and regional differences (Torre et al., 2015). Due to the lack of early detection techniques and effective therapeutic strategies, lung cancer remains the leading cause of cancer-related deaths worldwide (Roth and Diederichs, 2016). However, significant progress is underway in both the prevention and treatment of lung cancer (Hirsch et al., 2017). Recent studies have demonstrated the emerging roles of lncRNA in the development and progression of lung cancer. Here, we focus on the well-characterized lncRNAs in lung cancer.

MALAT1

MALAT1 (metastasis-associated lung adenocarcinoma transcript 1), also named NEAT2 (nuclear-enriched abundant transcript 2), is more than 8000 nt in length and is expressed from chromosome 11q13 (Ji et al., 2003). MALAT1 was reported to be processed by RNase P and RNase Z resulting a long nucleus-located MALAT1 transcript and a 61-nucleotide, cytoplasmic tRNA-like mascRNA (MALAT1-associated small cytoplasmic RNA). Wilusz et al. has demonstrated that mascRNA is a highly conserved small RNA that is broadly expressed in human tissues, but its biological function is unclear (Wilusz et al., 2008). MALAT1 was originally identified as a prognostic parameter for patient in stageINSCLC (Wilusz et al., 2008). Consistent with the conclusion, Schmidt et al. demonstrated that the MALAT1 expression level was associated with NSCLC patient survival and that MALAT1 possessed a tumor-promoting function (Schmidt et al., 2011). Survival analysis of a Chinese cohort revealed a genetic variant in MALAT1 that was associated with survival outcome (Wang et al., 2017a). Furthermore, MALAT1 was identified to have potential diagnostic value in early-stage NSCLC (Yao et al., 2012; Peng et al., 2016). The expression of MALAT1 was higher in the whole blood of lung cancer subjects with metastases compared to those without metastases. Elevated MALAT1 expression was detected in the serum exosomes isolated from NSCLC patients (Zhang et al., 2017b). Additionally, compared with blood from lung cancer patients with lymph node or pleura metastases, blood from those with bone or brain metastasis exhibited elevated MALAT1 expression (Guo et al., 2015b). *In vivo* and *in vitro* studies have also verified the important role of MALAT1 in bone metastases of NSCLC (Liu et al., 2016a). MALAT1 expression was induced in cancer stem cells (CSCs) and cisplatin-resistant cells, which indicated a role of MALAT1 in the resistance of lung cancers to chemotherapy (Lopez-Ayllon et al., 2014). MALAT1 knockdown suppresses metastasis both *in vivo* and *in vitro*, which adds a potential therapeutic approach to preventing lung cancer metastasis (Gutschner et al., 2013). In lung adenocarcinoma (LAD), MALAT1 was demonstrated to regulate the progression by targeting miR-204 (Li et al., 2016b). Schmidt et al. demonstrated that MALAT1 can interact with Bcl-2, whose expression is associated with a superior prognosis in localized NSCLC, which illustrated that MALAT1 could be used for risk prediction in NSCLC patients with resectable tumors. DNA methylation, TDP-43 and Oct4 were also implicated in regulating the expression of MALAT1 in NSCLCs (Guo et al., 2015a,c; Jen et al., 2017). Hypoxia, a hallmark characteristic of solid tumors, has been linked to energy metabolism. In hypoxic conditions, MALAT1 expression was demonstrated to be regulated by the CaMKK/AMPK/HIF-1α axis (Salle-Lefort et al., 2016). Advanced NSCLC patients with brain metastases often have a poor prognosis. MALAT1 was reported to promote lung cancer brain metastasis by inducing epithelial-mesenchymal transition (EMT) (Shen et al., 2015). Collectively, these studies have shown that MALAT1 has complex and extensive functions in the development and progression of lung cancer, and the use of genetic analysis for prognostic risk could help us to implement individualized treatment (Liu et al., 2017; Zhang et al., 2017a).

HOTAIR

HOTAIR (*HOX* transcript antisense RNA), which comprises 2158 nt, is transcribed in the antisense direction from the human *HOXC* locus on chromosome 12q13 (Rinn et al., 2007). The lncRNA HOTAIR can interact with histone methylase PRC2 and demethylase LSD1 (lysine-specific demethylase 1) by acting as a molecule scaffold to repress the *HOX* gene (Tsai et al., 2010). Emerging evidence has confirmed the role of HOTAIR in the promotion of proliferation, survival, invasion, metastasis, and drug resistance in lung cancer cells. This evidence indicates HOTAIR's potential in the diagnosis and treatment of lung cancer (Loewen et al., 2014; Yu and Li, 2015a). Elevated expression of HOTAIR has been detected in NSCLC tissues, and HOTAIR was demonstrated to enhance the aggressive behavior of NSCLC cells (Liu et al., 2013a; Nakagawa et al., 2013; Zhao et al., 2014). Using a three-dimension organotypic culture mode, Zhuang et al. revealed that tumor-promoting type I collagen (Col-1) upregulates the expression of HOTAIR in NSCLC cells (Zhuang et al., 2013). HOTAIR was demonstrated to promote the cisplatin resistance of LAD cells by downregulating p21 expression (Liu et al., 2013b, 2016b). *HOXA1* methylation was also indicated to be involved in the HOTAIR-mediated chemoresistance (Fang et al., 2016). Furthermore, HOTAIR was linked to cellular proliferation, invasiveness, and clinical relapse in SCLC (Ono et al., 2014). An *in vitro* study indicated that inflammation and EMT were mediated by HOTAIR, which could be the mechanism by which cigarette smoke extract induces lung carcinogenesis (Liu et al., 2015b). Of importance, HOTAIR is also involved in the miR-326-regulated cell proliferation and migration via targeting Phox2a (Wang et al., 2016c). Recently, a negative regulation loop of HOTAIR and p53 was identified in NSCLC cells. This revealed a new mechanism for the regulation of p53 in NSCLC cells (Zhai et al., 2016). HIF-1α inhibition was proven to prevent the upregulation of HOTAIR under hypoxic conditions (Zhou et al., 2015a). Radiotherapy was demonstrated to induce Lewis lung cancer cell apoptosis by upregulating HOTAIR through the inactivation of β-catenin (Chen et al., 2015). Wang et al. confirmed that HOTAIR was an important mediator of the ratio of FOXA1 and FOXA2, which suggested the inhibition might be a promising therapeutic option for LAD (Wang et al., 2015). In summary, HOTAIR contributes to diverse mechanisms that are involved in lung cancer, and more investigations could provide further insights into the biological function of HOTAIR.

H19

H19 is another widely studied lncRNA. It is expressed from chromosome 11p15.5, a region in which deletions have been frequently observed in human cancers (Doucrasy et al., 1993). H19 is transcribed by RNA polymerase II and is transported to the cytoplasm after sequential modification steps (Park et al., 2014). *H19* is a paternally imprinted and maternally expressed gene. H19 is highly expressed in embryonic tissues and in tumors but is postnatally inactivated in most tissues (Gabory et al., 2010). Shirley et al. first demonstrated *H19* and its upstream gene growth factor *IGF2* (insulin-like growth factor 2) had monoallelic expression in human tissues in 1993 (Rainier et al., 1993). Frequent loss of imprinting (LOI) of the gene *H19* was associated with lung cancer (Kondo et al., 1995). H19 was induced by the oncogene c-Myc, and H19 knockdown produced repression of the tumorigenic properties of lung cancer cells (Barsyte-Lovejoy et al., 2006; Zhang et al., 2016a). H19 was also induced under hypoxic stress in a p53-dependent manner (Matouk et al., 2010). H19 was shown to regulate the cell proliferation, migration, invasion and progression in lung cancer cells (Cui et al., 2015; Wang et al., 2016a). Supporting its potential role as an oncogene, higher levels of Mineral dust-induced gene (*MDIG*) and H19 expression correlated with poor survival in lung cancer patients (Chen et al., 2013). In LAD, the expression of H19 was correlated with cisplatin-resistance and clinical outcome, which indicated the role of H19 as a promising molecular maker (Wang et al., 2017b). In summary, H19 possesses a tumor-promoting activity, and its potential diagnostic and therapeutic uses in lung cancer require more fundamental and clinical studies.

MEG3

MEG3 (maternally expressed gene 3), also referred to as *GTL2* (gene trap locus 2) resides on the human chromosome 14q32. MEG3 is a widely expressed lncRNA in normal tissue, but it is significantly downregulated in NSCLC (Lu et al., 2013). As a tumor suppressor, MEG3 could regulate NSCLC cell proliferation and apoptosis through DNA methylation and activation of p53 (Lu et al., 2013). Bcl-xl and Wnt/β-catenin were demonstrated to be involved in the regulation of MEG3 in the cisplatin resistance of lung cancer cells (Liu et al., 2015a; Xia et al., 2015). Supporting its tumor suppressor role, MEG3 was shown to inhibit lung cancer cell growth through the MYC, Skp2 or Rb pathways (Yan-Hua et al., 2015; Kruer et al., 2016; Su et al., 2016). In LAD, MEG3 can function as a ceRNA to interact with miR-106, which then regulates MAPK9 to control the MAPK signaling pathway (Li et al., 2016a). MEG3 was demonstrated to have a crucial role in epigenetic regulation of the EMT process in lung cancer (Terashima et al., 2017). Zhou et al. discovered that exposure to the environmental carcinogen nickel led to downregulation of MEG3 by modulating the transcription of PHLPP1 (PH domain leucine-rich repeat protein phosphatase 1) and the translation of HIF-α (Zhou et al., 2017). Evidence from the GEO database showed that downregulation of MEG3 was correlated with an unfavorable prognosis in NSCLC (Zhang et al.,

2017c). A recent meta-analysis also revealed that MEG3 might serve as a novel prognostic factor in NSCLC patients (Wang et al., 2016b). In summary, MEG3 has been shown to inhibit lung tumorigenesis, but further study is needed to elucidate the underlying mechanism.

GAS5

The lncRNA GAS5 (growth arrest-specific 5) is transcribed from chromosome 1q25 and is ubiquitously expressed during embryonic development and in adult tissues (Coccia et al., 1992). *GAS5* was originally isolated from mouse genomic DNA and has been structurally characterized (Schneider et al., 1988). GAS5 is involved in several biological processes including proliferation, apoptosis, angiogenesis and tumor cell metabolism (Yu and Li, 2015b). GAS5 was identified as a tumor suppressor in NSCLC (Ma et al., 2016), and it is regulated by p53-dependent and p53-independent pathways (Shi et al., 2015). Compared with paired adjacent non-tumor tissue samples, GAS5 expression in LAD tissues was downregulated. Furthermore, low GAS5 expression was correlated with larger tumor sizes, poor tumor differentiation and advanced pathological stages. GAS5 was also shown to play a role in the development of the resistance to gefitinib (Dong et al., 2015). Additionally, GAS5 could modulate cisplatin sensitivity in NSCLC though various mechanisms (Zhang et al., 2016b; Cao et al., 2017). Knockdown of GAS5 in the LAD cell line A549, but not in the normal cell line BEAS-2B, affected the expression of its protein-coding targets CPS1 and AKR1C2 (Zhou et al., 2015b). GAS5 in the plasma was shown to be an ideal biomarker for NSCLC, which has considerable clinical value (Liang et al., 2016; Tan et al., 2017). In addition, GAS5 was shown to enhance radiosensitivity by repressing miR-135b in NSCLC (Xue et al., 2017). Furthermore, overexpression of GAS5 was able to inhibit tumorigenesis of NSCLC by suppressing miR-23a, which provided a novel therapeutic strategy for NSCLC (Mei et al., 2017). In addition to NSCLC, Renganathan et al. demonstrated that GAS5 expression in malignant pleural mesothelioma (MPM) was associated with cell quiescence and podoplanin expression, which supported a role for GAS5 in MPM biology (Renganathan et al., 2014). Thus, GAS5 demonstrates tumor suppression activity in lung cancer and is a promising therapeutic target.

Other lung cancer-related lncRNAs

In addition to the well-characterized lncRNA in lung cancer described above, other lncRNAs have also been demonstrated to show various functions in lung cancer. These include the onco-lncRNAs SOX2OT, ANRIL, CCAT2 and the tumor suppressor lncRNAs SPRY4-IT1, TUG1, BANCR and others (Sang et al., 2015). There is increasing evidence for aberrant regulation of lncRNAs in lung cancer. However, the regulatory mechanisms for most of the lncRNAs still need to be thoroughly characterized with regard to their use for the diagnosis and therapeutic intervention against lung cancer.

LncRNA in COPD

COPD (chronic obstructive lung disease) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation. The associated airway and/or alveolar abnormalities are usually caused by significant exposure to noxious particles or gases (Vogelmeier et al., 2017). The dysregulation of non-coding RNA, specifically miRNA, has been reported to be involved in the pathogenesis of COPD (De Smet et al., 2015). In contrast, there is limited information on the mechanisms of the regulation of lncRNA in COPD. Cigarette smoke exposure is the most important risk factor for the development of COPD. However, only approximately 20% of smokers develop COPD, which suggests that genetic and epigenetic factors contribute to the disease. Thai et al. discovered a novel long noncoding RNA, named smoke and cancer-related lncRNA-1 (SCAL-1), which was induced by cigarette smoke extract and was elevated in numerous cancer cell lines. SCAL-1 was determined to act downstream of NRF2 (nuclear factor erythroid 2-related factor) to mediate oxidative stress in airway epithelial cells (Thai et al., 2013). It is recognized that oxidant-antioxidant imbalance is a major component of the pathogenesis of COPD. Genome-wide analysis of the lung tissues of non-smokers without COPD, smokers without COPD and smokers with COPD revealed that altered expression of lncRNA was involved in the pathways that are implicated in the onset and progression of COPD (Bi et al., 2015). Microarray analysis of the lung tissues of COPD and non-COPD subjects identified abundant differentially expressed lncRNAs. An *in vitro* study further confirmed the role of TUG1 in mediating the expression of α-SMA and fibronectin in BEAS-2B and HFL1 cells (Tang et al., 2016a). Copy number variations (CNV) were demonstrated to play a role in COPD, potentially by altering the lncRNA HCG4B. Although the function of HCG4B remains elusive, the investigator speculated that HCG4B may regulate the expression of HLA-A, which has been proven to mediate the development of COPD by acting as a ceRNA to adsorb miR-122 and miR-1352 (Chen et al., 2017).

LncRNA in asthma

Asthma is a heterogeneous disease that is characterized by airway inflammation, reversible airway obstruction, airway hyperresponsiveness and airway remodeling (Reddel et al., 2015). Recent findings have highlighted the emerging role of noncoding RNA in the regulation of inflammation (Marques-Rocha et al., 2015). However, there are still a handful of investigations that have focused on the lncRNA-

associated regulatory mechanism in asthma. The proliferation and migration of airway smooth muscle cells (ASMC) contribute to the airway remodeling in asthma. A previous study linked the primary ASMC phenotype to the altered expression of selected lncRNA molecules including LINC00882, LINC00883, PVT1 (Perry et al., 2014). Austin and his colleagues isolated primary ASMC from healthy subjects and patients who were classified as having nonsevere and severe asthma, then investigated significant changes in lncRNA expression. Only one lncRNA (PVT1) was determined to decrease in patients with corticosteroid-sensitive nonsevere asthma and increase in patients with corticosteroid-insensitive severe asthma. Inhibition of PVT1 suppressed proliferation and IL-6 release in the ASMC from patients with severe asthma (Austin et al., 2017). These results implied that PVT1 might be an effective therapeutic target in reducing the airway remodeling in asthma (Yu et al., 2017). High expression of the lncRNA BCYRN1 was detected in an animal model of asthma, and an *in vitro* study confirmed its role in promoting the proliferation and migration of rat airway smooth muscle cells in asthma (Zhang et al., 2016c). Induced pluripotent stem cell (iPSC)-mesenchymal stem cells (MSCs) have been demonstrated to alleviate asthma. Aberrant lncRNA profiles were detected in induced asthma and iPSC-MSC treatment, which hinted at a role for lncRNA in the iPSC-MSC-mediated immunomodulation (Wang et al., 2017c). Severe asthma is associated with the activation of circulating CD8+ T cells. There is now emerging evidence that noncoding RNA is an important regulator of T-cell function. The expression of MEG3 and 18 additional lncRNAs was significantly altered in the CD8+ T cells from severe asthma patients (Tsitsiou et al., 2012). Glucocorticoid-resistant asthma is characterized by persistent airway inflammation that fails to resolve despite treatment with high doses of glucocorticoids. GAS5 has been found to act as a decoy for glucocorticoid receptors (Kino et al., 2010). Keenan et al. demonstrated that decreasing the GAS5 levels could enhance the glucocorticoid response of airway epithelial cells, which implied that GAS5 might emerge as a novel therapeutic target for restoring glucocorticoid sensitivity (Keenan et al., 2015). However, whether the expression of GAS5 is altered in asthma is unknown. An *in vivo* study also supported the role of lncRNA in therapy-resistant asthma. Compared to children with controlled persistent asthma, children with therapy-resistant asthma were determined to have upregulated expression of NEAT1 and PINT (AC058791.2), an lncRNA that is associated with p53 signaling (Marin-Bejar et al., 2013; Persson et al., 2015).

LncRNA in pulmonary fibrosis

Many lung diseases result in lung fibrotic remodeling. Idiopathic pulmonary fibrosis is the prototypical chronic, progressive fibrotic lung disease of unknown etiology that is characterized by increased fibroblast proliferation and activation. Differential expression of lncRNAs was observed in the bleomycin-induced rat lung fibrosis using microarrays. Two lncRNAs, named AJ005396 and S69206, were further validated by in situ hybridization (Cao et al., 2013). In a subsequent investigation, this laboratory team chose two differentially expressed lncRNAs, MRAK088388 and MRAK081523 to further explore the regulatory mechanism. MRAK088388 and MRAK081523 were demonstrated to mediate the expression of N4bp2 and Plxna4 by functioning as ceRNAs to adsorb miR-29b-3p and let-7i-5p, respectively (Song et al., 2014). In a bleomycin-induced murine model of pulmonary fibrosis, H19 was determined to promote EMT by interacting with miR-29b (Tang et al., 2016b). Sun et al. identified 513 lncRNAs that were upregulated and 204 lncRNAs that were downregulated in the paraquat-induced murine model of pulmonary fibrosis. In addition, overexpression

Table 1. Roles of lncRNAs in non-tumor lung diseases.

Disease	lncRNA	Expression	Target	Role of lncRNA	Location	Reference
COPD	TUG1	↑	-	inhibits proliferation and α-SMA and fibronectin	22q12	Tang et al., 2016a
asthma	PVT1	↑	miR-203a	promotes proliferation and IL-6 release	8q24	Austin et al., 2017; Yu et al., 2017
	BCYRN1	↑	TRPC1	promotes proliferation and migration of ASMC	Chr 9	Zhang et al., 2016
	MEG3	↑	-	-	14q32	Tsitsiou et al., 2012
	NEAT1	↑	-	-	-	Persson et al., 2015
	PINT	↑	-	-	-	Marin-Bejar et al., 2013
IPF	AJ005396	↑	-	-	-	Cao et al., 2013
	S69206	↑	-	-	-	Cao et al., 2013
	MRAK088388	↑	miR-29b-3p	mediates expression of N4bp2	-	Song et al., 2014
	MRAK081523	↑	let-7i-5p	mediates expression of Plxna4	-	Song et al., 2014
	H19	↑	miR-29b	promotes EMT	-	Tang et al., 2016b
	uc.77	↑	-	promotes EMT	-	Sun et al., 2016
	2700086A05Rik	↑	-	same as above	-	Sun et al., 2016
	CD99P1	↑	-	mediates proliferation and differentiation of lung fibroblasts	-	Huang et al., 2015
	n341773	↑	-	same as above	-	Huang et al., 2015

of uc.77 or 2700086A05Rik was found to regulate EMT in human lung epithelial cells (Sun et al., 2016). In another animal model of pulmonary fibrosis, the lncRNA cardiac hypertrophy-related factor (CHRF)-miR-489-MyD88 Smad3 signaling axis was demonstrated to exert a key function in silica-induced pulmonary fibrosis (Wu et al., 2016). Zhou et al. established a lipopolysaccharide (LPS)-induced mouse model to investigate the lung fibrosis in acute respiratory distress syndrome (ARDS), and lincRNA-p21 was determined to regulate the proliferation in lung fibrosis by inhibiting the expression of Thy-1 (Zhou et al., 2016). Nine lncRNAs were dysregulated in the tissues of human IPF patients, among which CD99P1 and n341773 were shown to be involved in mediating the proliferation and differentiation of lung fibroblasts (Huang et al., 2015). Ionizing radiation can induce lung fibrosis, and radiation-induced lung fibrosis (RILF) is a common side effect of thoracic irradation therapy (Roach et al., 1995). The lncRNA LIRR1 was shown to be upregulated in the X-ray-induced murine model of RILF. Furthermore, the DNA damage-response signaling mediated by lncRNA LIRR1 was linked to the molecular mechanism of this process.

LncRNA in pulmonary hypertension

Pulmonary arterial hypertension (PAH) is characterized by sustained elevated pulmonary arterial pressure and increasing vascular resistance, resulting in right heart failure. PAH comprises numerous clinical and pathophysiology entities with similar features but discrepant causes (Farber and Loscalzo, 2004). In a present study, the lncRNA and miRNA expression profiles of lymphocytes obtained from 12 idiopathic pulmonary arterial hypertension (IPAH) patients and 12 healthy controls were analyzed using microarray technique. 2,511 lncRNAs and 1,169 mRNAs were identified aberrantly expressed in IPAH patients, which indicated the involvement of dysregulated lncRNAs in the biological process of IPAH (Han et al., 2017). Chronic thromboembolic pulmonary hypertension (CTPH) is a type-4 pulmonary hypertension. Differential expression of 185 lncRNAs were observed in CTPH patients compared with healthy controls, among which NR_036693, NR_027783, NR_033766 and NR_001284 were significantly altered (Gu et al., 2015). This research provided evidence that lncRNA might be helpful for future study on diagnosis and management of CTPH. Hypoxia is a environmental factor associated with PAH (Farber and Loscalzo, 2004). A total of 362 lncRNAs were significantly altered in hypoxia pulmonary hypertension (HPY) rat model (Wang et al., 2016d). However, the specific regulatory mechanism of lncRNAs in HPY requires further in-depth research.

Conclusion

This review summarized the recent studies of well-characterized lncRNAs that are associated with lung cancer as well as lncRNAs that are involved in other non-tumor lung diseases. Previous studies have demonstrated the important role of lncRNAs in the pathogenesis of lung cancer. Further investigations into the biological functions of lncRNAs and how lncRNAs interact with their target DNA, RNA and proteins may offer novel diagnostic biomarkers and therapeutic targets for the treatment of lung cancer. It is clear that in contrast to the extensive studies of lncRNAs in lung cancer, few detailed lncRNA functions in non-tumor lung diseases have been elucidated (listed in Table 1), despite their importance. For instance, although IPF is usually considered to be a rare disease, it occurs with an incidence similar to that of stomach and brain cancers (Richeldi et al., 2017). IPF also shares a similarly disappointing prognosis with those of most malignant tumors with a 2-4-year median survival time from diagnosis. Furthermore, there is no effective treatment for IPF. Other non-tumor lung diseases including COPD, asthma and others also impose a huge burden on the world health care system. Additional fundamental research regarding non-tumor lung diseases is therefore urgently needed before lncRNA therapies can be available to the suffering patients. Recent studies have indicated roles for lncRNA in these non-tumor lung diseases. We predict that lncRNA will play important roles in the diagnosis and treatment of not only lung cancer but also non-tumor lung diseases. Because certain lncRNAs are expressed in a tissue-restricted manner (Guttman et al., 2010), we speculate that lncRNA-target treatment will be available for some respiratory diseases.

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