Long Noncoding RNAs in Non-Small Cell Lung Cancer: State of the Art

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Abstract Lung cancer is one of the most common malignancies worldwide. Despite a significant amount of basic and clinical research, mortality rates remain extremely high, especially for patients affected by advanced stage disease. Recently, new molecules playing several roles in the pathogenesis, diagnosis, and, potentially,

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clinical management of lung cancer are under investigation, including noncoding fragments of the human genome, also known as noncoding RNAs (ncRNAs). NcRNAs are commonly divided into two categories according to their size. The first category includes small ncRNAs, such as the recently discovered miRNAs, siRNAs, and the classical cellular RNAs (ribosomal, transfer, and other RNAs). Noncoding RNAs greater than 200 nucleotides represent a further category that includes long noncoding RNAs (lncRNAs). LncRNAs have numerous biological and pathophysiological effects. Numerous studies have recently investigated their involvement in the oncogenesis and the progression of pulmonary malignancies. In this chapter, we summarize the current knowledge regarding the role of lncRNAs in the pathogenesis, diagnosis, and clinical management of non-small cell lung cancer.

Keywords Lung · Cancer · NSCLC · LncRNA · Biomarkers

1 Introduction

Long noncoding RNAs (lncRNAs) are defined as autonomously transcribed noncoding RNAs that are longer than 200 nucleotides and have minimal coding potential. By contrast, noncoding transcripts with less than 200 nucleotides are defined as small noncoding RNAs (sncRNAs), which include micro-RNAs (miRNAs), small interfering RNAs (siRNAs), transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), and other classes of small RNAs. For a long time, the DNA sequence of lncRNAs was considered "junk DNA." Since the early 1990s, thousands of lncRNAs have been discovered and investigated; however, their exact number and role in human physiology and pathology are poorly understood. Recently, Hon et al. (2017) integrated multiple transcript collections using FANTOM5 cap analysis of gene expression (CAGE) data to generate a comprehensive atlas of 27,919 human lncRNA genes with high-confidence 5′ ends and expression profiles across 1829 samples from key human primary cell types and tissues.

On the basis of their extension and relation with coding genes on the DNA strands, lncRNAs can be broadly classified as genic (overlapping a protein-coding transcript at one or more nucleotides), nested (contained entirely within protein-coding transcripts), and intergenic (not overlapping a protein-coding transcript); other subtypes describe particular conditions (containing, overlapping, multiple relationships, etc.) (Ransohoff et al. 2018). In accordance with their level of activity, lncRNAs act at the transcriptional, posttranscriptional, and epigenetic level. At the transcriptional level, they have several functions including acting as decoys to disrupt the binding of transcriptional factors with promoters of target genes, altering the localization of transcriptional factors in the genome, competing with endogenous RNA, and forming scaffolds with DNA and proteins. At the posttranscriptional

level, they modulate directly or indirectly the effects of micro-RNAs (miRNAs) on target genes and regulate the alternative splicing of mRNA. At the epigenetic level, they interact with proteins involved in histone modifications, regulate DNA methylation in promoter regions, and interact with chromatin modification complexes (Wei and Zhou 2016).

Finally, on the basis of their specific molecular functions, lncRNAs act as molecular signal transducers, decoys, guides for ribonucleoprotein complex, scaffolds, and as sponge to sequester miRNAs (Peng et al. 2018). As signaling molecules, they serve as spatiotemporal indicators of gene regulation that reflect the biological effects of transcription factors (TFs) or signaling pathways; as decoys, they sequester TFs and other proteins away from chromatin or into nuclear subdomains; as guides, they recruit RNA-binding proteins to target genes; and as scaffolds, they recruit several proteins to form complexes with specific biological roles.

The reported functions have been described in several physiologic conditions and pathologies, including cancer (Palmieri et al. 2017). In particular, during the last decade, lncRNAs have been studied in the context of lung cancer, in order to better understand their roles in pulmonary carcinogenesis, and their potential application either as new therapeutic targets or as biomarkers for early diagnosis, prognosis, and therapy monitoring. This chapter provides an overview of the state of the art of current research on lncRNAs in the pathophysiology and clinical management of non-small cell lung cancer.

2 Lung Cancer: Current Status

Lung cancer is one of the most common malignancies and the leading cause of cancer-related deaths worldwide. In 2018, the International Agency for Research on Cancer (IARC) observatory estimated approximately 2,100,000 new cases and more than 1,700,000 deaths, a significant increase in comparison with previous estimations (Paliogiannis et al. 2013). The narrow gap between incidence and mortality rates highlights the challenges with early diagnosis and improving survival rates, especially in patients with advanced stage disease. Cancer Research UK reported recently that the 1-year overall survival rate is 32% for lung cancer patients, while the 5-year survival rate is around 10%. These figures suggest that there is a long way, in terms of basic and clinical research, to improve lung cancer survival rates.

Lung cancer includes a wide range of malignancies, which are broadly divided in small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The former is biologically, pathologically, and clinically different from other subtypes as it is characterized by aggressive behavior, early lymphatic and distant metastasis, and a high responsiveness to chemotherapy (Fig. 1). NSCLC, the focus of this chapter, comprises several further subtypes; the most common are adenocarcinoma (~50%), squamous cell carcinoma (~25%), and large cell carcinomas (~10%). Squamous cell carcinoma was the most common histotype until the 1980s when it was superseded

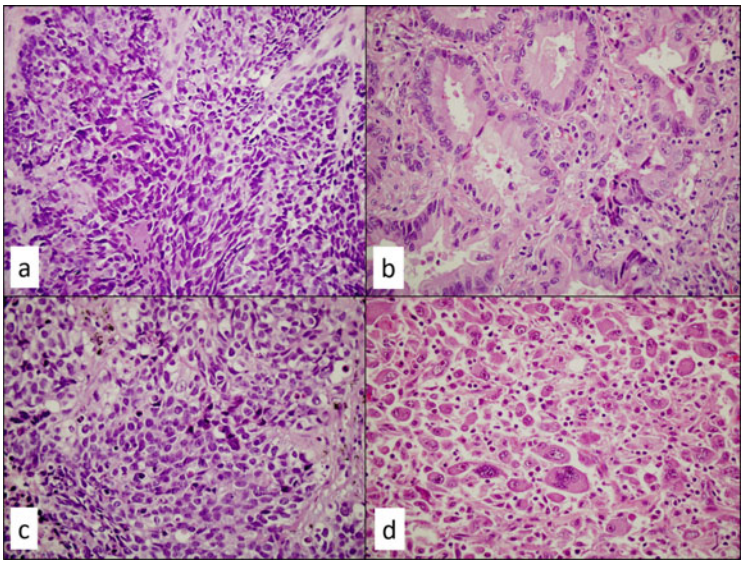

Fig. 1 The main histological subtypes of lung cancer. (**a**) Small-cell lung cancer, (**b**) adenocarcinoma, (**c**) squamous cell carcinoma, and d) large cell carcinoma. All samples are stained with hematoxylin and eosin and magnified at 40x

by adenocarcinoma. This might be explained by changes in smoking habits, particularly changes in the characteristics of cigarettes, increased puff volume, increased nitrate levels, and higher smoking incidence in women. Other than their morphological differences (Fig. 1), NSCLC subtypes show consistent differences in biological and clinical behavior, as well as different responses to current therapies, such as the recently introduced targeted agents.

Targeted therapies represent the most important innovation in the treatment of lung cancer over the last few years, also considering that surgical resection is an option in relatively a few cases. In 2004, activating mutations within the kinase domain of the epidermal growth factor receptor (EGFR) gene were discovered in lung adenocarcinomas, suggesting that these tumors were highly sensitive to tyrosine kinase inhibitors (TKIs), a class of agents that selectively inhibits the *EGFR* molecular pathway (Paliogiannis et al. 2015). TKIs such as gefitinib and erlotinib have been shown to significantly improve the clinical outcomes of approximately 40–60% Asian and 12–16% Caucasian patients with adenocarcinomas harboring *EGFR* mutations, with survival rates that were nearly twofold when compared to traditional chemotherapy (Shi et al. 2015). However, the increased frequency of resistance to TKIs reduced the initial enthusiasm around these agents, prompting at the same time further research to discover novel molecular targets and molecules with greater therapeutic efficacy and lower resistance rates. For example, additional agents, such as osimertinib, alectinib, and crizotinib, that target genetic alterations of the ALK and ROS1 genes have been introduced in clinical practice; these drugs

show a better ability to overcome resistance mechanisms in comparison to older medications. Other molecular targets such as KRAS, BRAF, HER2, MET, and RET, as well as their molecular pathways, are currently being investigated for the development of novel targeted agents (Colombino et al. 2019).

Immunotherapy with immune checkpoint inhibitors (ICIs) has been introduced more recently in NSCLC, further improving survival outcomes in patients with adenocarcinomas a well as in other NSCLC subtypes. Nivolumab, a monoclonal antibody targeting programmed death 1 protein (PD-1), was the first drug approved for advanced NSCLC not responding to platinum-based chemotherapy. Nivolumab showed durable responses in 10 (37%) of 27 confirmed responders with squamous NSCLC and 19 (34%) of 56 with non-squamous NSCLC that had ongoing response after a minimum follow-up of 2 years (Horn et al. 2017). Other agents, pembrolizumab and atezolizumab, are also gradually replacing standard chemotherapy as second- and first-line treatment in pan-negative advanced NSCLC. For ICIs, the expression of PD-L1 is currently considered as a major predictive factor for immunotherapy, despite some limitations in accurately selecting patients who would respond to treatment. Active research is ongoing to overcome such limitations, including the combination of immunotherapy drugs with different mechanisms of action, and their associations with targeted therapies.

3 LncRNAs in the Pathogenesis of NSCLC

A large number of studies reported abnormal patterns of expression of lncRNAs in NSCLC (Table 1). Specifically, these alterations promote molecular pathways that are involved in proliferation and migration, either by influencing second messengers' activation or triggering the transcription of growth factors. In this setting, lncRNAs are upregulated in neoplastic tissue and, in some studies, also in blood or plasma; their concentration may vary depending on the stage of the disease (presence of metastasis or tumor size). On the other hand, downregulated lncRNAs have also been described in tumor tissue. These lncRNAs promote cellular apoptosis through activation of proapoptotic genes or sequestration of pro-oncogenic molecules. Therefore, similar to protein-coding genes, lncRNAs can be classified as oncogenic or tumor suppressors.

3.1 Main LncRNAs with Oncogenic Functions

3.1.1 MALAT-1

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT-1*) is one of the first lncRNAs that was associated with lung cancer, especially with lung adenocarcinoma. *MALAT-1* is an 8.7 kB intergenic lncRNA (lincRNA) located on

Table 1 Biological activity of the main lncRNAs involved in the pathophysiology and clinical management of NSCLC

LncRNA	Main functions and effects
MALAT-1	Oncogenic: Alternative splicing of pre-mRNAs and chromobox homolog 4 (CXB4) regulation. Induces EMT. Worst prognosis and higher circulating levels in metastatic patients. Resistance to TKIs
HOTAIR	Oncogenic: Promotes gelatinases and suppresses metalloproteinases. Lower disease-free survival
CCAT2	Oncogenic: WNT signaling pathway. Induces Pokemon and suppresses p21. Increased levels in adenocarcinomas. Resistance to chemotherapies and radiotherapies
H19	Oncogenic: Induces the expression of JNK1/2. Poorer survival. Resistance to platinum-based chemotherapies
ANRIL	Oncogenic: ANRIL binds PCR2 and suppresses INK4A-ARF-INK4B. Higher expression in NSCLC tissues and in higher disease stages. Poorer survival
LUACT1	Oncogenic: Affects cellular growth. Correlates with cigarette smoking
SOX2-OT	Oncogenic: Affects expression of EZH2. Increased in squamous cell cancer
MEG3	Onco-suppressor: Induces cell apoptosis and impedes tumorigenesis. Upregulates p53. Low levels associated with bad prognosis and bad response to chemotherapy
TUG1	Onco-suppressor: Suppresses HOXB7 through PCR2. Resistance to paclitaxel
SPRY4-IT1	Onco-suppressor: Downregulated by EZH2. Lower levels in lung adenocarcinoma
GAS5	Onco-suppressor: Induces apoptosis. Low circulating levels in NSCLC patients. Predicts radiosensitivity
BANCR	Onco-suppressor: Inhibits EMT proteins. Decreased in NSCLC tissues. Correlations with stage and prognosis
TARID	Onco-suppressor: Activates TCF21 via GADD45A. Low levels in NSCLC
SCAL1	Induced by cigarette smoking. Regulated by NRF2. Upregulated in NSCLC
DQ786227	Malignant transformation in respiratory cells exposed to benzo(a)pyrene
LOC728228	Malignant transformation in respiratory cells exposed to benzo(a)pyrene

(continued)

Table 1 (continued)

LncRNA	Main functions and effects
CAR-10	Induced by air pollution. Upregulated by dibenz [a,h]anthracene, bounds (YB-1), and upregulates EGFR
NR-026689, XIST, HIF1A-AS1, lncRNA16, UCA1, RP11-397D12.4, AC007403.1, and ERICH1-AS1	Increased levels in NSCLC
LINC00313	Stage and histotype specific (squamous cell carcinomas)
RP11-21 L23.2, GPR158-AS1, RP11-701P16.5, and RP-11379F4.4	Poor prognosis
CTD-2358C21.4, RP11-94 L15.2, KCNK15. AS1, and AC104134.2	Better prognosis
AK126698 and ROR	Resistance to cisplatin chemotherapies. ROR induces resistance to radiotherapy
CNQ1OT1	Higher expression in paclitaxel-sensitive patients
BC087858	Activates PI3K/AKT and MERK/ERK. Induces EMT resistance to TKIs
pR-lncRNA-1, LINC-PINT, and TUSC7	Induce radioresistance
PVT1	Predicts radiosensitivity

chromosome 11q13. Silencing of *MALAT-1* in vitro reduces the mobility of lung adenocarcinoma cells. In alveolar basal epithelial cells (A549 cell line) and human NSCLC cells derived from lymph nodes (H1299 cell line), *MALAT-1* sponges miR206 promoting cellular invasion and migration (Tang et al. 2018). *MALAT-1* upregulation in lung cancer tissue is associated with metastasis progression and poor prognosis, particularly in early stage NSCLC patients with metastasis (Tano et al. 2010). Indeed, in patients with NSCLC and bone or brain metastases, the circulating concentrations of *MALAT-1* were found to be higher than in healthy individuals.

MALAT-1 transcription is regulated by p53, which is able to sequester its promoter. Although the activity of *MALAT-1* in lung carcinogenesis is not fully understood, two potential mechanisms of action have been described: (a) contribution to an alternative splicing of pre-mRNAs that produces an aberrant expression of genes such as B-MYB transcription factor, and (b) interaction with the demethylated chromobox homolog 4 (CXB4) that controls the relocation of growth-related genes in interchromatin granules. In addition, it has been reported that the CXC motif chemokine ligand 5 (CXCL5), as a downstream gene of *MALAT-1*, mediated the effects of *MALAT-1* on NSCLC migration and invasion (Guo et al. 2015).

3.1.2 HOTAIR

The HOX transcript antisense RNA (*HOTAIR*), a 2.4 kB antisense lncRNA located in chromosome 12, exhibits altered expression in several human cancers. In NSCLC cancer cells knocked out for *HOTAIR* in vitro, a decrease in proliferation and metastasis progression has been described. Experiments in fibroblasts showed that *HOTAIR* acts on homeobox D (a family of transcription factors) genes through epigenetic silencing: these genes are located in chromosome 2, where *HOTAIR* is driven to by polycomb repressive complex 2 (PCR2), a protein complex able to silence chromatin by methylation of histone 3 on lysine 27 (H3K27). *HOTAIR* acts as a scaffold binding to PCR2 and to lysine-specific demethylase 1 LSD-1/CoREST/REST complex. The LSD-1/CoREST/REST complex demethylates the lysine 4 of histone 3, resulting globally in chromatin rearrangement (Rinn et al. 2007). Furthermore, it has been demonstrated that *HOTAIR* promotes the expression of gelatinases and represses the expression of cell-adhesion proteins and metalloproteinases, promoting neoplastic cell motility and metastasis (Zhao et al. 2014); *HOTAIR* also suppresses $p21^{waf1}$ (discussed later) and HOXA5, a further protein involved in NSCLC cell migration and invasion. Taken together, these findings clearly support an important role of *HOTAIR* in NSCLC progression and metastasis. Nakagawa et al. (2013) confirmed that this lncRNA is associated with a shorter disease-free survival in patients affected by NSCLC.

3.1.3 CCAT2

The role of colon cancer-associated transcript 2 (*CCAT2*), an lncRNA first described in colorectal cancer, in carcinogenesis is not fully understood (Palmieri et al. 2017). *CCAT2* is a 1.7 kb intergenic lncRNA located on chromosome 8q24 that is involved in the WNT signaling pathway through an interaction with the transcription factor 7-like 2 (TCF7L2). This results in the upregulation of the expression of *MYC* and some miRNAs, such as miR-20a, known to regulate cell proliferation. A single nucleotide polymorphism (SNP) of *CCAT2*, rs6983267, has been associated with *CCAT2* overexpression. Zhao et al. (2018) showed that knockdown of *CCAT2* in NSCLC cells limited malignant growth and invasion, while artificial overexpression of *CCAT2* led to opposite effects. In addition, CCAT2 knockdown significantly decreased the expression of POK erythroid myeloid ontogenic factor (Pokemon) and induced the expression of the p21 tumor suppressor; this suggests that Pokemon overexpression could reverse the decrease of cell viability and cell invasion triggered by *CCAT2* silencing. In addition, *CCAT2* overexpression has been significantly associated with lung adenocarcinoma but not with squamous cell cancer. Silencing CCAT2 by siRNA has led to inhibition of proliferation and invasion in NSCLC cell lines in vitro (Qiu et al. 2014).

3.1.4 H19

Overexpression of *H19*, a 2.3 kb lncRNA located on chromosome 11p15 that is expressed only in the maternally inherited chromosome (imprinting phenomenon), is associated with poor prognosis in various cancers. *H19* overexpression is associated with hypomethylation of its promoter region; in NSCLC, this characteristic is frequently associated with loss of imprinting. *H19* induces cellular proliferation by stimulating the expression of c-Jun and c-Jun N-terminal kinase 1/2 (JNK1/2), and it acts as a sponge by sequestering let-7, a miRNA able to inhibit carcinogenesis by downregulating tumor-promoting proteins (e.g., RAS and MYC) (Kallen et al. 2013). Other pathophysiological mechanisms in lung oncogenesis have been also identified: miR-17/STAT3, miR-484/ROCK2, and miR-196b/LIN28B regulation, SAHH interaction and attenuation, and BPDE-DNA adduct formation. Several studies confirmed that the higher expression of *H19* was positively correlated with advanced tumor stage and tumor size, as well as that *H19* expression is an independent prognostic factor for overall survival of NSCLC (Chen et al. 2013).

3.1.5 ANRIL

Noncoding RNA in the INK4 locus (*ANRIL*) is a recently characterized lncRNA that is functionally correlated with the phospholipase D (PLD): the overexpression of *ANRIL* is associated with inhibition of PLD, with consequent anti-tumorigenic effects, while knockdown of *ANRIL* suppresses PLD inhibition-induced apoptosis (Kang et al. 2015). *ANRIL* is a 3.8 bp antisense lncRNA located on chromosome 9p21 which is transcribed from the INK4b-ARF-INK4a gene cluster and has been proven to be upregulated in multiple cancers, such as breast cancer, cervical cancer, nasopharyngeal carcinoma, and thyroid cancer. In tumorigenesis, *ANRIL* binds to PCR2 and causes a chromatin rearrangement and consecutive silencing of the INK4A-ARF-INK4B gene cluster, which contains tumor-suppressor genes also known as p16, p14, and p15. In addition, *ANRIL* has been proven to inhibit the expression of P21 and KLF2 and attenuate the transforming growth factor β (TGF-β)/Smad signaling pathway, promoting cancer invasion and metastasis. In recent studies, the expression level of *ANRIL* was higher in NSCLC tissues and lung cancer cells than in adjacent non-tumor tissues and normal human bronchial epithelial cells (Lu et al. 2016). The higher expression levels of *ANRIL* in NSCLC were positively correlated with advanced tumor-node-metastasis stage and had negative prognostic implications. Moreover, knockdown of *ANRIL* expression could inhibit lung cancer cell proliferation, migration, and invasion in vitro. For this reason, *ANRIL* has been recently investigated as part of promising panels for the diagnosis of NSCLC, which include other lncRNAs and traditional biomarkers such as the carcinoembryonic antigen (CEA) and the cytokeratin 19 fragment (CYFRA 21-1).

3.1.6 LUACT1 (SCAL1)

Lung cancer-associated transcript 1 is known also as smoke- and cancer-related long-chain noncoding RNA 1 (SCAL-1). It is located on chromosome 5 and it is typically tobacco-induced. The transcript includes four exons and three introns. *LUACT1* expression is transcriptionally regulated by nuclear factor erythroid 2-related factor (NRF2) and is determined by knockdown through siRNA in NRF2 and kelch-like ECH-associated protein 1 (KEAP1). Induction of *LUACT1* has been shown both in vitro and in vivo. It can play the downstream role of NRF2 in regulation of gene expression and intermediate in protection against oxidation stress in epithelial cells of the respiratory system. In a recent study, the lncRNA landscape in lung cancer has been characterized using publicly available transcriptome sequencing data from a cohort of 567 adenocarcinoma and squamous cell carcinoma tumors; functional validation, using both knockdown and overexpression, shows that the most differentially expressed lncRNA was *LUACT1* that was sufficient to affect cellular growth independently of other common cancer mutations (White et al. 2014).

3.1.7 SOX2-OT

SOX2 overlapping transcript (*SOX2-OT*) is an overlapping lncRNA located on chromosome 3 that is highly expressed in embryonic stem cells. Dysregulation of *SOX2-OT* has been observed in various tumors, including gastric cancer, esophageal cancer, breast cancer, hepatocellular carcinoma, ovarian cancer, pancreatic ductal adenocarcinoma, laryngeal squamous cell carcinoma, cholangiocarcinoma, osteosarcoma, nasopharyngeal carcinoma, glioblastoma, and lung cancer, wherein it typically functions as an oncogene and possibly as a tumor-suppressor gene. Hou et al. (Hou et al. 2014) showed that the expression level of *SOX2-OT* in 53.01% of human primary lung cancer was twofold higher than that in pair-matched adjacent non-tumor samples. Compared to adenocarcinomas, *SOX2-OT* expression was significantly higher in squamous cell carcinoma of the lung. Knockdown of *SOX2-OT* inhibited cell proliferation by decreasing the number of cells in S phase and inducing G2/M arrest. The protein expressions of EZH2 and cyclin B1 and Cdc2 were reduced, and ectopic expression of EZH2 restored the G2/M transition and cyclin B1 and Cdc2 protein expression (Hou et al. 2014). Further studies demonstrated that *SOX2-OT* expression was obviously higher in NSCLC tissues and serum samples than in normal controls and that *SOX2-OT* overexpression was associated with poor survival in patients with lung cancer.

3.2 Main LncRNAs with Onco-suppressive Functions

3.2.1 MEG3

Low concentrations of the lncRNA maternally expressed 3 (*MEG3*) correlate with poor prognosis in NSCLC (Zhou et al. 2012). *MEG3* is a 6.9 kb lncRNA located on chromosome 14q32, expressed only in the maternal-inherited chromosome. It is expressed in normal human tissues, especially in brain and the pituitary, and is thought to be a tumor suppressor. Recent studies showed that *MEG3* expression is disrupted in various human cancers, such as bladder cancer, glioma, and hepatocellular carcinoma. In lung cancer, *MEG3* upregulates p53 expression, inhibiting the exon 3 ubiquitin ligase from preventing p53 transcription. It can also act as a guide for PCR2, bringing it to the regulatory regions of target genes. Interestingly, its overexpression has different effects in in vitro and in vivo experiments: in vitro overexpression induces cell apoptosis, whereas in vivo overexpression inhibits tumorigenesis. A recent report demonstrated that expression of *MEG3* in NSCLC cell lines was negatively correlated with miR-205-5p, which enhances cell proliferation and represses apoptosis through targeting low-density lipoprotein (LDL) receptor-related protein-1 (LRP1) (Wang et al. 2017a). Other reports showed that *MEG3* expression was decreased in NSCLC tumor tissues compared with normal tissues and associated with advanced pathological stage and tumor size. Moreover, patients with lower levels of *MEG3* expression had a relatively poor prognosis.

3.2.2 TUG1

The concentration of the lncRNA taurine-upregulated gene 1 (*TUG1*) in squamous carcinoma and adenocarcinoma is negatively associated with advanced disease stage and shorter overall survival. *TUG1* is a 5.6 kb intergenic lncRNA located on 22q12 chromosome that was originally identified in a genomic screen of taurine-treated mouse retinal cells. *TUG1* has been demonstrated to serve crucial regulatory roles in various cancer-associated biological processes. It binds to PRC2 in the promoter region of CELF1 and negatively regulates CELF1 expression. It guides PCR2 into the homeobox B7 region (HOXB7), an oncogene responsible for activating both the PI3K/ERK and MAPK pathways, resulting in an increase in cellular proliferation (Zhang et al. 2014). PCR2 suppresses the expression of HOXB7. *TUG1* expression is mediated by wild-type *p53*; this effect is lost in cases of *p53* mutations with R175H missense substitution. *TUG1* is found to exhibit aberrant expression in a variety of malignancies. Dysregulation of *TUG1* has been shown to contribute to proliferation, migration, cell cycle changes, inhibited apoptosis, and drug resistance of cancer cells which revealed an oncogenic role for this lncRNA, but some reports have shown downregulation of *TUG1* in lung cancer samples compared with noncancerous samples. Interestingly, in NSCLC patients, *TUG1* downregulation correlated with sex, smoking status, and tumor differentiation grade.

3.2.3 SPRY4-IT1

Sprouty homolog 1 4 intronic transcript 1 (*SPRY4-IT1*) is derived from an intron of the SPRY4 gene located in chromosome 5q31.3. Its downregulation, due to transcriptional repression mediated by EZH2, a histone methyltransferase able to induce a H3K27 modification, favors cell migration and invasion in vitro. By contrast, its upregulation induces apoptosis and, in mice, reduces metastasis. In a recent study, *SPRY4-IT1* expression was observed to be significantly lower, and the expression of EZH2 significantly higher, in lung adenocarcinoma tissues when compared to the adjacent normal tissues (Wen et al. 2018). *SPRY4-IT1*-suppressed expression in NSCLC is correlated with larger tumor size and lymph node metastasis.

3.2.4 GAS5

Growth arrest specific 5 (*GAS5*) is an lncRNA located in chromosome 1q25, involved in inducing apoptosis. In recent studies, the expression pattern of *GAS5* was investigated in NSCLC specimens and healthy tissues, and its biological functions in the development and progression of NSCLC were assessed. *GAS5* expression was downregulated in cancerous tissues compared to adjacent noncancerous tissues and was highly related to tumor size and stage. Furthermore, *GAS5* overexpression increased tumor cell growth arrest and induced apoptosis in vitro and in vivo. In addition, siRNA-mediated knockdown of *GAS5* promoted tumor cell growth. It has been demonstrated that the ectopic expression of *GAS5* significantly upregulates p53 expression and downregulates transcription factor E2F1 expression. In addition, upregulation of GAS5 in NSCLC cells was able to suppress their growth, migration, and invasion via the miR-205/PTEN axis. Therefore, GAS5 is a tumor suppressor in NSCLC which acts through p53-dependent and p53-independent pathways. A recent study showed that *GAS5* circulating concentrations are reduced in NSCLC patients but tend to normalize after surgical resection of the tumor (Liang et al. 2016). The authors found that *GAS5* expression levels could distinguish NSCLC patients from control patients with 82.2% sensitivity and 72.7% specificity and that the combination of the *GAS5* and carcinoembryonic antigen could produce an area of 0.909 (95% confidence interval 0.857–0.962) under the receiver-operating characteristic curve in distinguishing NSCLC patients from control subjects.

3.2.5 BANCR

BRAF-activated noncoding RNA (*BANCR*) is a 693-bp lncRNA on chromosome 9 that is overexpressed in melanoma cells and crucial for melanoma cell migration. In a recent study, overexpression of BANCR was found to play a key role in epithelial-mesenchymal transition (EMT) through the regulation of E-cadherin,

N-cadherin, and vimentin expression (Sun et al. 2014). In this study, BANCR expression was significantly decreased in 113 NSCLC tumor tissues compared with normal tissues. Additionally, reduced BANCR expression was associated with larger tumor size, advanced pathological stage, metastasis distance, and shorter overall survival of NSCLC patients. Finally, reduced BANCR expression was found to be an independent prognostic factor for NSCLC.

3.2.6 TARID

TCF21 antisense RNA inducing demethylation (TARID) has been demonstrated to activate TCF21 expression by inducing promoter demethylation. This occurs because TARID interacts with both the TCF21 promoter and GADD45A (growth arrest and DNA-damage-inducible, alpha), a regulator of DNA demethylation. In a pilot study, TARID was downregulated in NSCLC cells and tissues, but its potential pathophysiological and clinical roles need to be further elucidated (Arab et al. 2014).

3.3 LncRNAs and Endothelial to Mesothelial Transition (EMT)

EMT is described as a reversible phenomenon in which an epithelial cell loses its distinctive characteristics and becomes a mesenchymal cell through the activation of different pathways that culminates in loss of E-cadherin. EMT plays a crucial role in the pathogenesis of NSCLC. It is believed that EMT represents one of the mechanisms of resistance to target therapies in NSCLC patients; moreover, EMT and subsequently mesothelial to endothelial transition (MET) could represent a key process that allows lung cancer cells to metastasize. Numerous lncRNAs have been demonstrated to be involved in EMT, particularly *MALAT-1*, *HOTAIR,* and *SPRY4-IT1*. As discussed earlier, *MALAT-1* concentrations in peripheral blood are higher in patients with brain metastases, suggesting a possible role in inducing EMT. In particular, *MALAT-1* upregulation increases ZEB1/2 and decreases E-cadherin levels concentrations in these patients.

HOTAIR is able to bind to PCR2, a protein complex needed for H3K27 trimethylation that contains the histone methyltransferase EZH2, which in turn represses E-cadherin gene by H3K27 methylation (Cao et al. 2008). *SPRY4-IT1* and *BANCR* act in similar ways as previously discussed.

4 LncRNAs and Lung Cancer Risk Factors

Altered concentrations of lncRNAs have been described in relation to well-known risk factors for lung cancer, especially cigarette smoking. The most studied is smoking cancer-associated lncRNA 1 (*SCAL-1*) which is induced by cigarette smoking and is upregulated in NSCLC cell lines (Thai et al. 2013). This lncRNA, located in chromosome 5, is regulated transcriptionally by nuclear factor erythroid 2-related factor (NRF2). As previously discussed, cigarette smoking initially induces upregulation of the active H19 allele. This is likely to progress to loss of imprinting as the burden of smoking increases and as the epithelium undergoes transition from normal to neoplastic. The *lncLUACT1*, previously described, also correlates with cigarette smoking, while lncRNA *DQ786227* and lncRNA *LOC728228* are involved in malignant transformation in respiratory cells exposed to benzo(a)pyrene (Gao et al. 2013; Hu et al. 2015). Finally, lncRNA *CAR-10* is upregulated in NSCLCs due to a different risk factor for NSCLC—air pollution. This lncRNA is upregulated by a polycyclic aromatic hydrocarbon, dibenz[a,h]anthracene (a pollutant of smoke and oils), that increases the expression of FoxF2. CAR-10 bounds and stabilizes transcription factor Y-box-binding protein 1 (YB-1), leading to upregulation of the EGFR and proliferation of lung cancer cells (Wei et al. 2016).

5 LncRNAs as Diagnostic and Prognostic Biomarkers

5.1 LncRNAs as Diagnostic Biomarkers

The high interest gained by lncRNAs in cancer is also related to their putative role as diagnostic biomarkers for early diagnosis of tumors and/or for differential diagnosis of specific malignancies. This would be particularly relevant in NSCLC in order to improve the currently low survival rates. From this perspective, lncRNAs have some features that make them suitable as potential biomarkers: as previously discussed, the tissue or blood concentrations of some of them change in relation to either the presence of the tumor, its stage, or prognosis; others are tissue-specific, and their concentrations change in particular NSCLC histotypes. Furthermore, they can also be determined in other biological fluids, particularly pleural effusions, frequent in NSCLC patients. The most relevant issue against the implementation of specific lncRNAs detection in clinical practice is represented by their generally low concentrations in biological fluids, which prevents easy determination with standard analytical methods. Concentrations and types of lncRNA detected also vary depending on the biological sample (whole blood, serum, and plasma); to date, there are no NSCLC-associated lncRNA recognized in sputum.

Whole blood concentrations of several lncRNAs are altered in NSCLC patients (Table 1). For the discrimination of NSCLC patients from cancer-free controls, MALAT-1 showed a sensitivity of 56% and a specificity of 96% in cellular fractions

of whole blood (Weber et al. 2013). Hu et al. (2015) reported that circulating SPRY4-IT1, ANRIL, and NEAT1 were significantly increased in plasma samples of NSCLC patients. Receiver operating characteristic curve (ROC) analysis revealed that plasma ANRIL provided the highest diagnostic performance with an area under ROC curve value (AUC) of 0.798. Combination of the three factors further increased the diagnostic performance (AUC, 0.876; sensitivity, 82.8%; specificity, 92.3%). Other lncRNAs, particularly *NR-026689*, *XIST, HIF1A-AS1*, *lncRNA16*, *UCA1*, *RP11-397D12.4, AC007403.1,* and *ERICH1-AS1,* have been shown to be increased in NSCLC patients. On the other hand, blood concentrations of onco-suppressive lncRNAs, particularly GAS5, BANCR, and TARID, are generally lower in NSCLC patients.

Currently, none of the molecules described is used in clinical practice due to the technical reasons mentioned above and the need to better establish their predictive capacity (sensibility, specificity, positive and negative predictive values) through adequately designed clinical trials. In some cases, combination of lncRNAs with traditional biomarkers may be effective. Qiu et al. (2014) showed that CCAT2 combined with CEA could predict lymph node metastasis in NSCLC patients. Currently, one clinical trial conducted in China is recruiting patients to evaluate the role of lncRNAs as potential biomarkers for lung cancer diagnosis [NCT03830619].

The association between blood concentrations of some lncRNAs and stage of the disease is also of interest. For example, *LINC00313*, an intergenic lncRNA, can be detected in serum of patients affected with T2N1-stage lung adenocarcinoma (Li et al. 2015). Another interesting feature of some lncRNAs is their histotype specificity. Even if NSCLC subtypes present specific morphologic, immunohistochemical, and molecular characteristics, the exact diagnosis may be difficult in some cases. Biomarkers detectable in serum specific for NSCLC histotypes would be useful in this context. In a study that compared lncRNAs expressed in lung adenocarcinoma and lung squamous cell carcinoma tissues, *LINC01133* was upregulated in lung squamous cell carcinomas, but not in adenocarcinomas (Zhang et al. 2015). Conversely, Qiu et al. (2014) reported that *CCAT2* overexpression is significantly associated with lung adenocarcinoma, but not with squamous cell cancer.

5.2 *LncRNAs as Prognostic Markers*

Most of the lncRNAs described have been found to be related to the prognosis of the disease, despite their obscure role in NSCLC pathogenesis. For example, *RP11-21 L23.2*, *GPR158-AS1*, *RP11-701P16.5,* and *RP-11379F4.4* were correlated with poor overall survival, while *CTD-2358C21.4*, *RP11-94 L15.2*, *KCNK15.AS1,* and *AC104134.2* were related to better overall survival (Zhou et al. 2015). Also, low expression of some lncRNAs is associated with prognosis: for example, low concentrations of MEG3, GAS-6AS1, and other onco-suppressing molecules correlate with poor overall survival (Han et al. 2013).

6 LncRNAs in NSCLC Therapy

Some lncRNAs have shown to be implied in lung cancer therapy, both for their implications in acquired or non-acquired therapy resistance and for their possible use as therapeutic targets.

6.1 Role of LncRNAs in Resistance to Therapy

6.1.1 Resistance to Chemotherapy

The development of resistance to chemotherapy, for example, cisplatin, is commonly observed in lung cancer. A different expression profile of 1380 lncRNAs was found in vitro in A549 cells and cisplatin-resistant A549/CDDP cells, suggesting that lncRNAs are involved in chemotherapy resistance mechanisms (Yang et al. 2013). Cisplatin acts by inhibiting DNA replication and damaging cell membrane, leading to apoptosis. Resistance may arise because of altered expression of lncRNAs, which can reactivate proliferation pathways and/or repair cisplatin-induced damage. *AK126698* targets Wnt, while *lncROR* targets PI3K/AKT/mTOR, increasing sensitivity to cisplatin-based therapies (Shi et al. 2017). HOTAIR hyperexpression induces cisplatin resistance by downregulating the cyclin-dependent kinase inhibitor 1, a protein associated with cell cycle arrest, and upregulating the expression of stem cell-related biomarkers such as Klf4 (Liu et al. 2016). Furthermore, H19 plays a role in platinum therapy resistance by regulating apoptosis proteins such as BAX, BAK, and FAS (Wang et al. 2017b). Furthermore, patients with downregulation of MEG3 exhibit reduced response to cisplatin therapy, probably because MEG3 is able to modulate the expression of p53, activate the Wnt/β-catenin pathway, and sponge regulatory miRNAs.

Two lncRNAs were found to be associated with altered response to paclitaxel: *CNQ1OT1*, which exhibits increased expression in lung adenocarcinoma cells that are paclitaxel-sensitive (Ren et al. 2017), and TUG1, by influencing EZH2 in lung squamous cell carcinoma (Niu et al. 2017).

6.1.2 Resistance to Targeted Therapy

Some lncRNAs can affect the efficacy of anti-EGFR TKIs by inducing alterations which allow cancer cells to "escape" their effects, resulting in an acquired resistance to therapy and disease progression. *UCA1* expression, upregulated in patients with EGFR-TKIs resistance, activates the AKT-mTOR pathway and stimulates EMT (Cheng et al. 2015). The lncRNA *BC087858* also induces EGFR-TKIs resistance by activating the PI3K/AKT and MERK/ERK pathways, as well as inducing EMT (Pan et al. 2016). *lncBC0587858* induces EMT by upregulating FOXC1, leading to

E-cadherin inhibition and induction of EMT (Xia et al. 2013). *MALAT-1* promotes EMT through EMT-associated transcription genes and activation of the Wnt pathway (Samatov et al. 2013).

6.1.3 Resistance to Radiotherapy

Mechanisms of radioresistance are still largely unknown. Some studies suggested a modulation by noncoding RNAs principally in response to DNA damage, radiation-associated cell death, hypoxia, and activation of cancer stem cells. The ncRNAs responsible for these events are predominantly miRNAs; however, some lncRNAs are also involved, particularly *lncROR*, *pR-lncRNA-1*, *LINC-PINT,* and *TUSC7*. In mice lung cancer models, upregulation of *HOTAIR* is associated with a decreased radiosensitivity by the inactivation of the β-catenin pathway (Chen et al. 2015). LncRNAs may be also suitable as markers of response to radiotherapy: the lncRNA plasmacytoma variant transcript 1 (*PVT1*) and the *lncGAS5* have been demonstrated to serve as putative biomarkers in predicting radiosensitivity (Wu et al. 2017; Xue et al. 2017).

6.2 LncRNAs as New Therapeutic Targets

The comprehension of the pathogenic roles of lncRNAs in lung carcinogenesis is essential in order to investigate and establish new therapeutic targets. Numerous studies have been published to date (the most important are summarized in this chapter), and several interactions between lncRNAs and the main molecular pathways involved in lung carcinogenesis have been explored, evidencing opportunities for novel therapies. It is in principle possible to modulate the action of lncRNAs by blocking these interactions with siRNAs, antisense oligonucleotides, ribozyme, and aptamers. As previously discussed, these methods have been employed to inhibit oncogenic lncRNAs in several studies, with encouraging results. For example, experimental silencing of *MALAT-1* with antisense oligonucleotides in mouse models reduced lung cancer metastasis (Gutschner et al. 2013). Nevertheless, there are currently no clinical trials testing lncRNA-targeting agents suggesting that additional research is warranted.

7 Conclusions and Future Perspectives

NSCLC is currently the leading cause of cancer-related death worldwide. Despite recent advances in the surgical and clinical management, mortality rates remain extremely high and close to incidence rates. Therefore, further research is warranted to improve survival, especially in the advanced stages of the disease. LncRNAs

represent an emerging class of noncoding RNAs, which show encouraging results and potential applications in the diagnosis of NSCLC and in predicting the prognosis in subgroups of patients. In particular, numerous lncRNAs have been evaluated as biomarkers for early diagnosis, differential diagnosis, and stage stratification of NSCLC patients with encouraging results. Nevertheless, their clinical applicability and their predictive potential have to be tested with methodologically tailored studies. Furthermore, recent evidence strongly suggests that some lncRNAs or their combinations can predict either sensitivity or resistance to cisplatinum-based chemotherapy and TKI-based treatments, which further impacts prognosis. In this context, lncRNAs might be proposed as biomolecular markers for patient selection and implementation of personalized oncological treatments and for establishing alternative therapeutic strategies in cases of prediction of resistance to these treatments.

Currently, there are no available biomarkers to implement such a task, with the exception of some somatic mutations, such as the T790M *EGFR* mutation which determines resistance to TKIs in patients with lung adenocarcinoma. These mutations can be absent in the initial diagnosis and develop subsequently during treatment. This dictates the need to monitor the mutational status of driver and resistance-conferring genes during the course of the disease. Liquid biopsy methods are being developed to this regard, but they harbor several limitations, mainly due to technical reasons. In this setting, the use of lncRNAs might be useful for the prediction of sensitivity/resistance to therapies; however, their detection in biological fluids is challenging due to instability, which imposes the use of novel techniques.

Finally, lncRNAs can be molecular therapeutic targets themselves, considering their involvement in several pathophysiological mechanisms of lung cancer. Unfortunately, these small molecules are involved in numerous complex physiological and pathological processes, which currently limits their potential as targets. Further research is warranted to understand the interactions between lncRNAs and other classes of molecules to better elucidate their potential implication in the treatment of NSCLC.

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