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Chapter

Tumour Suppressor Genes with Oncogenic Roles in Lung Cancer

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Abstract

Lung cancer is one of the most common cancers and the leading cause of cancer-related deaths worldwide. High-throughput sequencing efforts have uncovered the molecular heterogeneity of this disease, unveiling several genetic and epigenetic disruptions driving its development. Unlike oncogenes, tumour suppressor genes negatively regulate cell cycle control and exhibit loss-of-function alterations in cancer. Although tumour suppressor genes are more frequently disrupted, oncogenes are more likely to be drug-targeted. Many genes are described as presenting both tumour suppressive and oncogenic functions in different tumour types or even within the natural history of the disease in a single tumour. In this chapter, we describe current knowledge of tumour suppressor genes in lung tissues, focusing on tumour suppressor/oncogene duality.

Keywords: tumour-suppressor genes, oncogenes, dual roles, lung cancer, targeted therapy

1. Introduction

Cancer cells arise in non-malignant tissue due to the sequential acquisition of molecular alterations that drive proliferation, permit the evasion of growth suppression and apoptosis signals and promote angiogenesis, invasion and metastasis [1]. This process is stochastic, and over time the tumour continues to evolve in a dynamic manner, generating a group of cells harbouring different genetic and epigenetic features [2]. The resulting heterogeneity is the basis of tumour evolution and leads to the selection of tumour cells. These cells often present with rewired signalling networks and often oncogene addiction [3].

The uncontrolled growth of cancer cells can in part be explained by their aberrant gene expression patterns. While most cancer genes are characterized as either oncogenes or tumour suppressors based on their typical behaviour in tumours, some genes display dual oncogenic and tumour suppressive functions [4, 5]. The majority of these genes encode multiple isoforms, which are further post-translationally modified and form a variety of protein complexes, generating a context-dependent cellular network [6]. In diploid organisms, gain-of-function (GOF) mutations in oncogenes are typically dominant (single events are sufficient to promote tumourigenesis), while loss-of-function alterations are recessive in TSGs

(requires two inactivation events) [7]. For example, for a TSG with dual oncogenic roles, one gain-of-function mutation can potentially cease its tumour suppressive function and turn on oncogenic signalling [5].

Recently, genes with both oncogenic and tumour-suppressive functions were described across 12 main cancer types using The Cancer Genome Atlas (TCGA) database [5]. Using a text mining approach, the authors identified genes mainly represented by kinases (e.g. *BCR*, *CHEK2*, *MAP2K4*, *NTRK3* and *SYK*) or transcription factors (e.g. *BRCA1, EZH2, NOTCH1, NOTCH2, STAT3* and *TP53*) and evaluated them at the genomic and gene expression levels. Using an *in silico* analysis, it was shown that genes with dual functions interact with more partners and are more important hub-genes in protein-protein interaction networks.

In this chapter, we discuss TSGs with both tumour suppressive and oncogenic functions in lung cancer.

1.1 Lung cancer classification

Lung cancer is one of the most common cancers and the leading cause of cancer-related deaths worldwide [8]. In the United States, lung cancer accounts for 13.5% of all new cancer cases and 25.3% of all cancer deaths. The five-year survival rate is dismal, with only 18.6% of patients surviving 5 years [9]. The majority of lung cancer cases (approximately 80%) are attributed to cigarette smoking [10]. About 10–25% of cases occur in people who have never smoked [11]. The aetiology behind these cases is most likely a combination of genetic factors, as well as the effects of exposure to environmental carcinogens such as asbestos, radon gas or other forms of pollution [12].

Lung cancer is classified according to histological type. There are two major types: small cell lung cancer (SCLC), which accounts for 15–20% of lung cancer patients, and non-small cell lung cancer (NSCLC), comprising the remaining 80–85% (**Figure 1**) [13]. SCLC, primarily originating from the central airways, is thought to be derived from neuroendocrine cells [14]. NSCLC is composed of three major histological
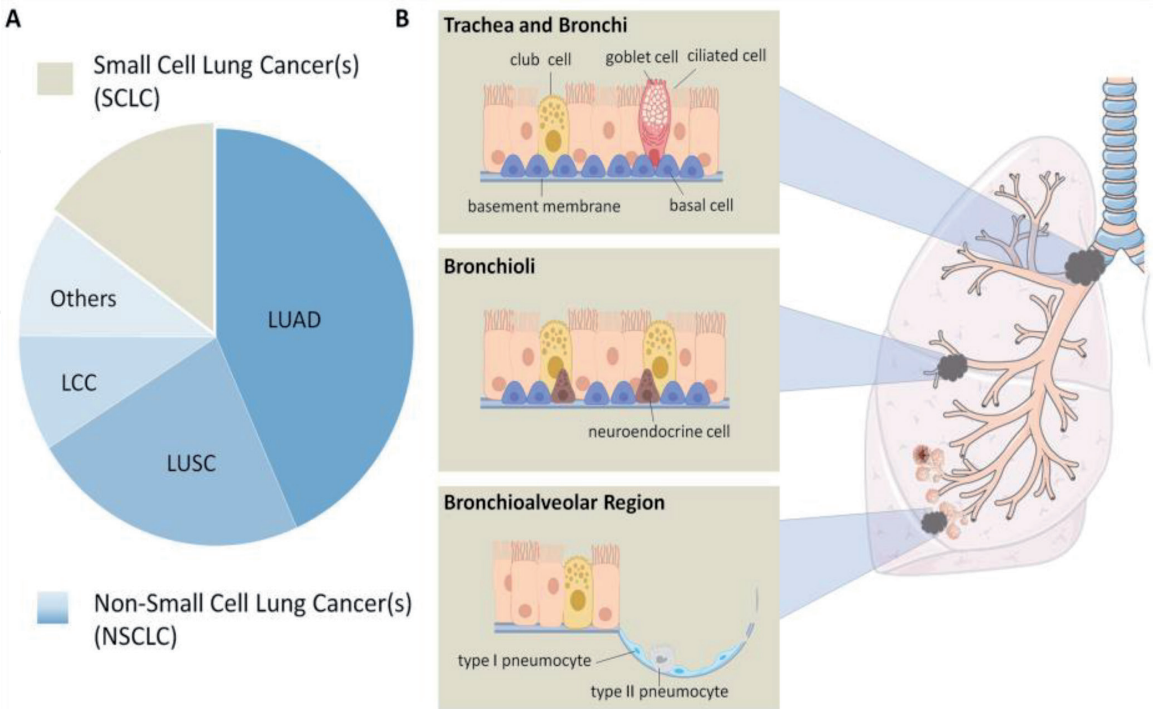
Figure 1.
Histological classification of lung cancer. (A) Lung cancer histological types. (B) Location of the tumours and cell origins. SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; LCC, large cell carcinoma.
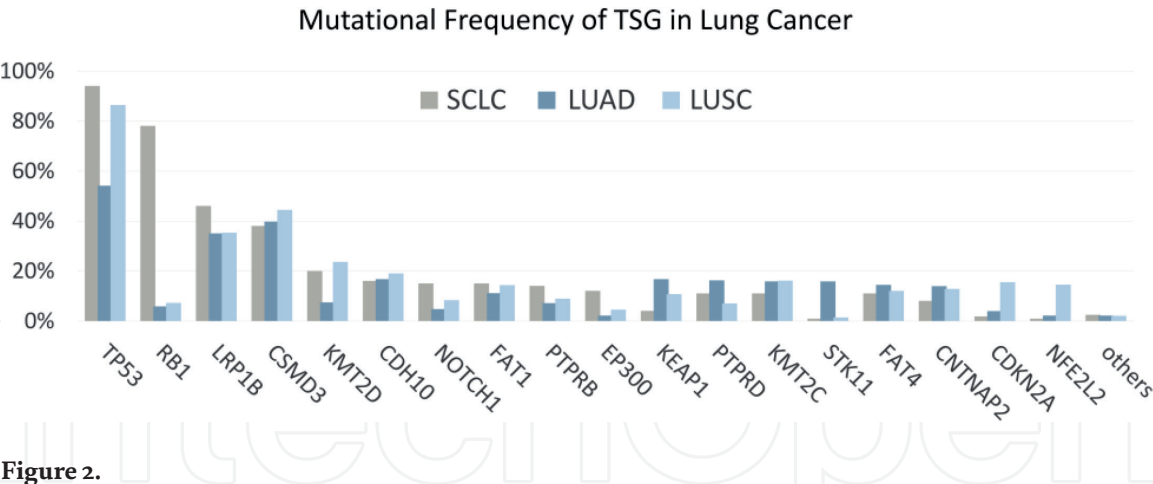
Figure 2.
Mutational frequency of TSGs in small cell lung cancer (SCLC; n = 110) [16], lung adenocarcinoma (LUAD; n = 660) [23] and lung squamous cell carcinoma (LUSC; n = 484) [23]. TSGs were defined according to COSMIC Cancer Gene Census (https://cancer.sanger.ac.uk/census) and mutation frequency of the most commonly disrupted TSGs in these subtypes of lung cancer were retrieved using cBioPortal (http://www. cbioportal.org/).

subtypes: adenocarcinoma (LUAD), squamous cell carcinoma (LUSC) and large cell carcinoma (LCC). LUAD is the most common, accounting for approximately 40% of all lung cases [15]. LUAD typically arises from glandular epithelium, from bronchioalveolar stem cells, club (Clara) cells or type II pneumocytes in the lung periphery [13]. LUAD is also the predominant subtype that arises in patients who have never smoked [15]. LUSC develops primarily in the central airways and segmental bronchi, strongly associates with a history of smoking and accounts for approximately 20% of all lung cancer cases. LCC may arise anywhere in the lung and are classified as tumours without general features associated with SCLC, LUAD or LUSC [13].

1.2 TSG mutation spectrum in lung cancer

Beyond the histological heterogeneity of lung cancer, genomic studies of large cohorts have uncovered the complex molecular landscape of lung tumours. Indeed, it has been observed that a wide variety of oncogenes and TSGs can be altered in lung cancer, and these molecular events are vastly different between histological subtypes [16, 17].

Clinical studies have shown that molecularly defined lung cancer subgroups can correlate with characteristics such as ethnicity [18], smoking history [19], treatment sensitivity [20] or prognosis [21]. Many of the commonly identified gain-of-function alterations in proto-oncogenes have been actively investigated for therapeutic purposes. For example, *EGFR, ALK, ROS1, BRAF, MET, RET* and *HER2* are routinely assessed in the clinic to offer targeted therapy for eligible LUAD patients [22].

Three TSGs are frequently mutated in all three major lung cancer subtypes: *TP53, LRP1B* and *CSMD3*. Other TSGs of particular interest in lung cancer are as follows *RB1* and *CREBBP* in SCLC, *KEAP1* and *STK11* in LUAD, *CDKN2A* in LUSC, *NOTCH1* and *PTEN* in both SCLC and LUSC and NF1 in both LUAD and LUSC (**Figure 2**). Mutations in these TSGs are usually mutually exclusive, indicating that individual genes are capable of driving lung cancer progression.

2. TSGs with oncogenic roles in lung cancer

Several TSGs in lung cancer have also been shown to behave as oncogenes, depending on the molecular context and/or the mechanism by which they are

altered (**Table 1**). Among them are *TP53*, *NFIB*, members of the NOTCH family, *NKX2-1*, *NFE2L2*, as well as some non-coding RNAs (*MALAT1*, *mir*-125, and *mir*-378), which will be discussed in detail below.

2.1 *TP53*

TP53 is a well-known TSG, representing the most common somatically mutated gene in human cancer, especially in lung tumours [24]. The classic functions of the encoded p53 protein are cell cycle regulation, DNA repair, senescence mediated by stress, apoptosis and angiogenesis. These functions mainly occur through

Gene	Main function	Role as TSG	Role as oncogene
TP53	TF: regulates cell cycle, DNA repair, senescence and apoptosis	TSG in several tissues: frequently lost through mutations [24]	Missense mutations confer gain-of-function oncogenic properties [31]
NFIB	TF: crucial in lung development	Underexpressed in NSCLC and associated with poor survival in LUAD [32]	Amplified and OE in SCLC: inducing chromatin reprogramming during metastasis [33]
NOTCH1/NOTCH2	Transmembrane receptors: proliferation, differentiation and survival	Inactivated by inhibitor ligands and through mutations, especially in SCLC [34]	Maintains stem cell features; promotes proliferation in LUAD [35]
NFE2L2	TF: cellular defense mechanism against oxidative stress	Protects lung tissue against exposure to oxidative stress [36]	Mutational activation: aids cells to escape from endogenous tumour suppression [37]
NKX2-1	TF: essential for lung development	Acts as a TSG in *KRAS*-driven p53-mutant LUAD [38]	Enhanced oncogenic signals in *EGFR*-driven LUAD [39]
STK11	Serine-threonine kinase: regulation of energetic metabolism and cell polarity	Mutational inactivation promotes cancer development [40]	OE maintains metabolic homeostasis and attenuates oxidative stress [40]
TGFB	Cytokine: regulates development, differentiation and homeostasis	Expression loss leads to growth arrest in early-stage lung and other cancers [41]	OE promotes tumour growth in advanced cancer stages [42]
TUSC3	Endoplasmic reticulum protein in magnesium uptake, glycosylation and embryonic development	Hypermethylation; expression loss in NSCLC; inhibits cell proliferation and promotes apoptosis [43]	OE in NSCLC accelerates cancer growth; induces EMT [44]
WT1	TF: role in urogenital system development	Loss of function enhances cell viability and proliferation in Wilms' tumour [45]	OE promotes survival in *KRAS*-mutated NSCLC [46]
MALAT1	Long non-coding RNA	OE reduces invasiveness in PTEN expressing tumours [47]	OE associated with chemotherapy resistance in NSCLC [48]
miR-125b	microRNA	OE induces apoptosis [49]	OE promotes metastasis [50]
miR-378	microRNA	OE reverses chemoresistance to cisplatin in LUAD [51]	OE is associated with invasion and brain metastasis [52]

TF, transcription factor; OE, overexpression; EMT, epithelial-mesenchymal transition. Numbers in brackets refer to the list of reference.

Table 1.
Main TSGs with dual functions reported in lung cancer.

the binding of a p53 tetramer to the promoter of target genes [25]. In many cancer types, *TP53* mutation is associated with poor prognosis, including local and distant metastases events, resistance to treatment and decreased survival [26, 27].

Despite having a reputation as a 'guardian of the genome', recent work has shown that activating *TP53* alterations can act to promote cancer development and progression [25, 28]. Depending on the location of the mutation within the *TP53* gene, protein structure and subsequent DNA binding activity can be lost or altered, resulting in either loss or gain of function [25]. In contrast to the majority of TSGs, *TP53* is not commonly inactivated by deletions or truncating mutations. Indeed, 74% of mutations within the *TP53* locus are missense point mutations, which can be found in proteins in human tumours [25]. In fact, altered *TP53* was initially considered as a cancer antigen with putative oncogenic properties [25]. Together, this highlights the dichotomous role of *TP53* disruptions, in that both the loss of wild-type p53 and gain-of-function mutations can provide a growth advantage to tumours [28].

Lung cancer is commonly associated with tobacco use, where the prolonged exposure to carcinogens damages the DNA of the exposed cells. These alterations are especially enriched in missense mutations in *TP53*, leading to GOF-p53 [29]. The oncogenic GOF mutation in p53 was previously shown to be related with the inactivation of AMP-activated protein kinase (AMPK) signalling in head and neck cancer and another tobacco-related cancer [30]. AMPK is a master regulator of metabolic homeostasis and GOF-mutated p53 is able to physically interact and inhibit AMPK, stimulating aerobic glycolysis under energetic stress conditions and leading to invasive growth.

In lung cancer mouse models, prevention of tumour formation by inhibiting GOF p53 mutants has been demonstrated [53]. Although the highly aberrant genomes in p53-mutated tumours should lead to unfeasible mitosis, these mutations facilitate the survival and proliferation of these cells through stabilizing replication forks and promoting micronuclei arrangement [31].

GOF p53 mutants are most likely involved in multiple mechanisms that coordinate tumour progression. For example, GOF-p53 (R175H, R273H and D281G) was demonstrated to upregulate *CXCL5, CXCL8* and *CXCL12* through its transcription factor activity, promoting migration of lung cancer cell lines [54]. *CXCL5* expression was shown to be elevated in human lung tumour samples harbouring GOF-p53, and its inhibition could reverse cell motility in lung cancer and melanoma cell lines [54]. In NSCLC, it was recently reported that GOF-p53 can physically interact with HIF-1 and binds to the SWI/SNF chromatin remodelling complex, inducing the expression of hypoxia-responsive genes [55]. Importantly, specific extracellular matrix components are upregulated by this process and mediate pro-tumourigenic features in NSCLC [55].

2.2 *NFIB*

Nuclear factor I (NFI) is a transcription factor family, comprising NFIA, NFIB, NFIC and NFIX, that plays important roles in normal development and in numerous diseases [56]. These proteins bind to specific DNA sequences leading to repression or activation of gene expression in a context-dependent manner, regulating cell differentiation and proliferation through their target genes [57]. *NFIB*, in particular, has been implicated in a wide range of malignancies, being described as both an oncogene and a potential TSG [58].

Using an *in vivo* model, it was demonstrated that NFIB is a metastatic driver in SCLC, inducing global chromatin reprogramming during metastasis [33]. The authors isolated tumour cells from primary and metastatic sites of genetically engineered mice, and using genome-wide analysis, they showed a pronounced increase

in chromatin accessibility during tumour progression, resulting from *NFIB* copy number amplifications. Interestingly, the distal regions that became accessible upon *NFIB* upregulation were similar to open regions found in neural tissue. Recently, the same group described two metastatic models in SCLC, one dependent and other independent of *NFIB* amplification [59]. *NFIB* was likewise reported as amplified and/or overexpressed in melanoma [60], breast [61], oesophagus [62] and salivary gland malignancies [63].

A gene fusion involving *NFIB* (*MYB-NFIB*) is frequently found in adenoid cystic carcinomas from salivary glands [64] and in adenoid cystic carcinoma from other topologies [65]. Despite the putative oncogenic function of *NFIB*, studies have focused on its fusion partner *MYB* as the main oncogenic driver in these cancers [66]. Given the fact that other fusion partners of *NFIB* have been reported in adenoid cystic carcinomas [67] and that *MYB-NFIB* fusions lead to *NFIB* truncation [68], *NFIB* may have a possible independent role as a TSG in these malignancies.

While the *MYB-NFIB* fusion is not observed in lung cancers, *NFIB* is frequently underexpressed in NSCLC tissues [32] and during epithelial-to-mesenchymal transition in NSCLC cell lines [69]. NFIB is an essential transcriptional factor in lung development [70] and was demonstrated to be targeted by many microRNAs that recapitulate their foetal lung expression patterns in NSCLC [32]. Lower expression of this gene was associated with shorter overall survival, less-differentiated tumour features and repressed expression of cell differentiation markers in LUAD patients [32]. Therefore, contrary to the established oncogenic role of NFIB in SCLC, these observations suggest a tumour suppressive role in NSCLC.

2.3 *NOTCH* gene family

The Notch signalling pathway is important in the regulation of cell fate during embryogenesis and maintenance of homeostasis in adult tissues [71]. It includes Notch receptors (NOTCH1, NOTCH2, NOTCH3 and NOTCH4) and ligands from the DSL family, which suppress or induce tumour-related mechanisms under specific cellular contexts [71].

In SCLC, Notch signalling is frequently inactivated by either a mutation in Notch receptors or the overexpression of ligands that inhibit downstream signalling [34]. Despite this potential role as a TSG, Notch signalling in lung tumours is complex, as it has also been shown to be related to chemoresistance in SCLC [72]. In addition, the overactivation of this pathway through several mechanisms acts like an oncogene in LUAD by preserving stem cell features and promoting proliferation [35, 73]. Notch1 expression is required in Kras-driven LUAD carcinogenesis, suppressing apoptosis via the p53 pathway [35]. The inhibition of the Notch pathway is able to restrain lung cancer stem cell maintenance, which is characterized by subpopulations of cells expressing aldehyde dehydrogenase [74].

Conversely, loss-of-function mutations of Notch receptors generating truncated receptors imply a TSG role in LUSC [75]. Although functional studies to further corroborate this hypothesis are still needed, reports in other squamous cell carcinomas substantiate the idea that the inactivation of this signalling pathway promotes tumourigenesis [76].

2.4 *NKX2-1* (also known as *TTF-1*)

Nkx2-1 is a homeobox-containing transcription factor that is essential for lung development and is expressed in type II pneumocytes and bronchiolar cells in adults [77]. It is expressed in 40–50% of lung cancers and is amplified and overexpressed in 6–11% of LUAD [78].

Nkx2-1 acts as a lineage-specific oncogene in some LUAD cases [79], enhancing cell viability and proliferation in lung cancer cell lines [78]. This function relies on the activation of (i) the pro-survival PI3K-AKT pathway, through ROR1 kinase-dependent c-Src activation as well as maintaining the EGFR-ERBB3 association [80], and (ii) LMO3, a member of the LMO family of oncogenes that is translocated in T-ALL [81].

On the other hand, *Nkx2-1* expression has been associated with good patient outcome [82] and the loss of *Nkx2-1* expression was associated with the aggressive behaviour of NSCLCs [83]. Mechanistically, tumour suppressive functions of Nkx2-1 in lung adenocarcinoma rely on the restriction of cell motility, invasion and metastatic ability, through the inhibition of the TGF-β [41] and IKK-B/NFk-B [39] pathways. The dual role of Nkx2-1 is dependent on *EGFR, KRAS* and *TP53* status in LUAD: *NKX2-1* acts as a TSG in *KRAS*-driven and *TP53*-mutant tumours, whereas it enhances *EGFR*-driven tumourigenesis [84, 85].

2.5 *NFE2L2*

NFE2L2 encodes a transcription factor that regulates proteins involved in cellular defense mechanisms against metabolic, xenobiotic and oxidative stress [86]. *NFE2L2* has been often considered a TSG due to its protective role against genome-damaging agents, the higher propensity to cancer development in *NFE2L2*-deficient mice and its protective effects in cancer chemoprevention [87].

Due to the constant exposure to oxidative stress in the lung, the *NFE2L2* pathway is important to guarantee the genomic stability of these cells [88]. However, once transformation of normal to cancer cells occurs, *NFE2L2* favours tumour development by acting to protect against oxidative stress resulting from the tumour microenvironment and exposure to genotoxic agents during patient treatment [86]. In fact, mutations in *NFE2L2* and *KEAP1,* an important member of the *NFE2L2* signalling, are very common and mutually exclusive in NSCLC [89]. Curiously, a recent study demonstrated that lung cancer patients presenting *NFE2L2* or *KEAP1* mutations are highly resistant to chemotherapy [89]. However, the relation between the *NFE2L2* pathway and treatment response prediction needs further investigation.

2.6 *MALAT1* and other non-coding RNAs

While large-scale genomic sequencing efforts have uncovered an invaluable number of genetic alterations related to cancer biology, in the past, they were commonly focused on the 2% of the genome that encodes protein [90]. In the last decade, non-coding RNA transcripts have been shown to have important regulatory functions in normal and disease biology [91]. Indeed, many non-coding genes have been shown to play tumour-suppressive or oncogenic roles in numerous cancer types [92].

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) was one of the first cancer-related long non-coding RNAs to be described [93]. *MALAT1* is broadly expressed in normal cells, where it has been shown to regulate the alternative splicing of pre-mRNAs by changing the distribution of splicing regulators in nuclear speckles [94]. *MALAT1* was primarily identified as an oncogenic transcript in lung cancer and has since been widely considered a marker of metastasis, poor patient survival [93] and chemotherapy resistance in NSCLC [48]. Mechanistically, *MALAT1* has been shown to promote carcinogenesis through P53 deacetylation [95] and enhance cell migration through Akt/mTOR signalling [96] and TGF-β-induced endothelial-to-mesenchymal transition [97]. Conversely, *MALAT1* has also been shown to reduce invasiveness by modulating the expression of EpCAM and ITGB4 in PTEN-expressing tumours [47] and by downregulation of MMP2 and inactivation

of ERK/MAPK signalling [98]. *MALAT1* also binds the nuclear p65/p50 heterodimer and thus inhibits NF-κB-dependent pathways [99] and is thought to be involved in the response to DNA damage [100]. Furthermore, *MALAT1* reduces the invasiveness of cerebral metastases by sustaining the blood-brain barrier [101]. *MALAT1* expression and subcellular location is finely tuned through various regulatory mechanisms [102], which may drive its pro- or anti-tumour effects [103]. Analysis of the dual role of *MALAT1* highlights not only the complexity of non-coding RNA function but also their relevance to broad areas of cancer biology and management.

MicroRNAs (miRNAs) are short transcripts that typically regulate coding genes post-transcriptionally through direct interaction with mRNA transcripts. Many are deregulated in lung cancer [104], where they have documented tumour-suppressive and oncogenic roles [105]. For example, miRNA-125b has been shown to have a multifaceted function as a tumour suppressor and oncogene, being underexpressed in bladder [106] and ovarian cancer [107] and overexpressed in glioma [108] and prostate cancer [109]. It was shown that miRNA-125b induces apoptosis in cancer cell lines exposed to nutrient starvation and chemotherapy, including in lung cancer [49]. On the other hand, miRNA-125b may also function as an oncogene in NSCLC, as it is able to promote metastasis by targeting TP53INP1 [50]. In addition, inhibition of miR-125b can also decrease the invasive potential and leads to cell cycle arrest and apoptosis in NSCLC [110]. Similarly, miR-378 was reported to be overexpressed in lung cancer and other tumour types, inducing cell migration, invasion and tumour angiogenesis [111]. However, it was previously demonstrated that upregulation of this miRNA sensitizes lung cancer cell lines to cisplatin [51].

3. Conclusions and future directions

Here, we summarize the commonly disrupted genes in lung cancer with dual roles as both tumour suppressors and oncogenes. These conflicting roles are a result from the complexity of biological pathways and the heterogeneity of cancer cells.

Most of the current molecular therapies are based on hyperactivated oncogene inhibitors. In lung cancer, only a fraction of the cases exhibit alterations in targetable genes, such as *EGFR, BRAF* and *MET* mutations and *ALK, RET* and *ROS1* fusions [112]. Therefore, there is an urgent need for the development of novel therapeutic strategies exploiting non-oncogene alterations of lung tumour cells.

Considering that TSGs are found altered more frequently than oncogenes in human tumours [113], the existence of TSGs with dual oncogenic roles opens a new window of opportunities for the development of new targeted therapies. However, therapeutic action against TSGs remains challenging, as many are not amenable to current pharmacologic inactivation strategies. Most of the TSGs are not a kinase that can be pharmacologically blocked and are not located at the cell surface to be targeted by an antibody.

In summary, there is an unmet need to clarify the ambiguity found within genes, both coding and non-coding, with both pro- and anti-tumour functions. Broadening our understanding of these features may enable the development of novel and specific therapeutic strategies that consider both molecular and tissue contexts.

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Conflict of interest

The authors have no conflicts to declare.

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