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Review

Molecular mechanisms underlying the regulation of tumour suppressor genes in lung cancer

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ABSTRACT

Tumour suppressor genes play a cardinal role in the development of a large array of human cancers, including lung cancer, which is one of the most frequently diagnosed cancers worldwide. Therefore, extensive studies have been committed to deciphering the underlying mechanisms of alterations of tumour suppressor genes in governing tumourigenesis, as well as resistance to cancer therapies. In spite of the encouraging clinical outcomes demonstrated by lung cancer patients on initial treatment, the subsequent unresponsiveness to first-line treatments manifested by virtually all the patients is inherently a contentious issue. In light of the aforementioned concerns, this review compiles the current knowledge on the molecular mechanisms of some of the tumour suppressor genes implicated in lung cancer that are either frequently mutated and/or are located on the chromosomal arms having high LOH rates (1p, 3p, 9p, 10q, 13q, and 17p). Our study identifies specific genomic loci prone to LOH, revealing a recurrent pattern in lung cancer cases. These loci, including 3p14.2 (*FHIT*), 9p21.3 ($p16^{INK4a}$), 10q23 (*PTEN*), 17p13 (*TP53*), exhibit a higher susceptibility to LOH due to environmental factors such as exposure to DNA-damaging agents (carcinogens in cigarette smoke) and genetic factors such as chromosomal instability, genetic mutations, DNA replication errors, and genetic predisposition. Furthermore, this review summarizes the current treatment landscape and advancements for lung cancers, including the challenges and endeavours to overcome it. This review envisages inspired researchers to embark on a journey of discovery to add to the list of what was known in hopes of prompting the development of effective therapeutic strategies for lung cancer.

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1. Introduction

Globally, lung cancer is the second most frequently diagnosed cancer after breast cancer, preceding colorectal, prostate, and stomach cancers, according to GLOBOCAN 2020. Lung cancer tops the list as the leading cause of cancer death with both genders combined, accounting for nearly one fifth (18%) of the total cancer deaths [1]. In the United States, lung and bronchus cancer ranks third in the list of the common types of cancer, after breast and prostate cancers. According to estimates from the Surveillance, Epidemiology and End Results (SEER) in 2022, lung and bronchus cancer represents 236,740 of new cases (12.3% of all new cancers) and 130,180 of new cancer deaths (21.4% of all cancer deaths). The age-adjusted incidence rate of lung cancer was 52.0 per 100,000 men and women per year based on 2015–2019 cases, with men having a higher rate than women (58.9 vs 46.8 per 100,000). In the United States, lung and bronchus cancer is the leading cause of cancer death, with a death rate of 26.7 per 100,000 men and women per year. As with the incidence rate, the death rate per 100,000 persons per year was also higher for men than women of all races, with a death rate of 44.5 and 30.7, respectively. The SEER data from 2012 to 2018 reported that the 5-year survival rate in the United States was 22.9%. Lung and bronchus cancer is more prevalent and is associated with the elderly population; based on the 2015–2019 cases, the median age at diagnosis and death for lung and bronchus cancer as 71 and 72 years, respectively. Nevertheless, the age-adjusted cancer incidence and death rates have been declining on an average of 2.1% and 3.7% each year from 2010 to 2019, respectively [2]. This encouraging trend may be attributed to the emergence of better diagnosis and screening methods, such as the implementation of biomarkers in clinical samples to facilitate early detection [3]; and effective treatments such as chemotherapy, immunotherapy and targeted therapy that have been shown to improve survival rates [4].

1.1. Association between tobacco smoking and lung cancer risk

Tobacco smoking is the main culprit of lung cancer deaths in 76% and 40% of men and women in 2019, respectively [5]. The Million Women's Study and the British Doctors Study reported findings that the all-cause mortality rate of current smokers was three times that of non-smokers. These studies also showed that smoking resulted in two-thirds of all deaths of smokers and provided evidence that, smoking cessation before age 30 years could avoid almost all the excess risk [6,7]. Tobacco consumption rate, age at initiation, intensity, duration, cessation, composition, smoking behaviour are chief determinants of lung cancer risk among smokers. A study confirmed that cigarette smoking duration is a more significant predictor of lung cancer risk than smoking intensity, regardless of age and gender [8]. This was supported by other studies showing that smoking duration as assessed by years is more strongly associated with lung cancer compared with the number of cigarettes smoked per day [9,10]. A study on 50-year trends (year 1959–2010) in smoking-related mortality in the United States based on gender found that the relative risks of smoking-related deaths (e.g., lung cancer, COPD, and ischemic heart disease) were identical in both female and male smokers in the 2000–2010 period [11]. A systematic review and meta-analysis also reported similar findings that both women and men conferred similar risks for smoking-related lung cancer, with a women-to-men relative risk ratio of 0.81 in current smokers [12]. These results supported the notion that, the women's life-time smoking behaviours are becoming increasingly similar to that of men with regard to begin smoking at an earlier age [13], which results in higher cumulative exposure [12]. Interestingly, the 50-year trends study also reported that there was an increase in mortality rate from COPD in both male and female smokers compared to never-smoker from the 1960 s to year 2010. This may be attributed to the changes in cigarettes design since the 1950 s that promote deeper inhalation, resulting in increased exposure of tobacco carcinogens to lung parenchyma [11]. Indeed, the evolution of cigarette designs, including filters and chemical composition may have contributed to the histology subtype of lung cancer [11]. Smoke from unfiltered cigarettes is inhaled shallowly and results in the deposition of chemical carcinogen in the central (trachea and bronchus) area, giving rise to squamous cell carcinoma. On the other hand, filtered, low-tar cigarettes are deeply inhaled, resulting in deposition at the lung periphery giving rise to adenocarcinoma [14,15]. Therefore, the switch from unfiltered to filtered cigarettes may explain the predominance of peripheral adenocarcinomas and a corresponding decrease in squamous cell carcinomas since the 1970 s [11]. Intriguingly, lung squamous cell carcinoma is more common in men, whereas adenocarcinoma is the predominant lung cancer subtype in women [14,16]. This may be due to the fact that women begin smoking cigarettes a few decades later than men, and they mainly smoked on the modern, low tar cigarettes [17].

1.2. Types of lung cancer

Lung cancers can be categorized histologically into two main types: small cell lung cancer and non-small cell lung cancer. Small cell lung cancer (SCLC) accounts for 15–20% of lung cancer with strong predilection for early metastasis and poor prognosis [18]. The 2015 World Health Organization (WHO) Classification of Tumors grouped SCLC with other lung neuroendocrine tumours, such as carcinoid tumours, typical carcinoid, atypical carcinoid, and large cell neuroendocrine carcinoma (LCNEC). SCLC is a high grade, malignant epithelial tumour consisting of small cells with a round-to-spindle shape, scant cytoplasm, finely granular nuclear chromatin, and inconspicuous nucleoli [19]. SCLCs are often associated with exposure to tobacco carcinogens and the decrease in risk upon smoking cessation is the strongest, compared to other types of lung cancer [20,21]. Tumour protein p53 (*TP53*) and retinoblastoma 1 (*RB1*) are the most commonly altered tumour suppressor genes in SCLCs, with a frequency of 94.3% and 91.4%, respectively [22].

SCLC shows good responsiveness to initial chemotherapy; however, majority of the patients will develop chemoresistance on disease recurrence and die from distant metastasis [23,24]. Treatment for SCLC depends on the cancer stage. For instance, in the rare occasion where the patients are presented with limited-stage SCLC (LS-SCLC) at the time of diagnosis, the standard of care treatment is chemotherapy with concurrent radiotherapy [18]. Other treatment options may include surgery, fractionated radiotherapy, and stereotactic ablative body radiotherapy (SABR) [25]. Majority of the patients with extensive stage SCLC (ES-SCLC) are presented with distant metastases at the time of diagnosis, and the principal treatment is systemic chemotherapy alone [26]. However, prophylactic cranial irradiation (PCI) may be indicated for patients who are chemoresponsive and has been shown to increase patient's overall survival (OS) and decrease brain metastases [26,27]. Over the decades, the first-line treatment for ES-SCLC has always been the doublet regimen of platinum-based chemotherapy (cisplatin or carboplatin combined with etoposide) [28]. However, due to the frequent incidences of tumour remission with this treatment regimen [23], numerous clinical trials have been carried out in search for potential therapeutic agents to treat relapsed SCLC [29]. The only US Food and Drug Administration (FDA)-approved chemotherapeutic agent for second-line treatment for relapsed SCLC is topotecan (topoisomerase I inhibitor) [30]; amrubicin (topoisomerase inhibitor II) is only approved for use in Japan, as its superiority to topotecan in terms of improving OS was only demonstrated in Japanese but not in western patients with relapsed SCLC [31,32].

Non-small cell lung cancer (NSCLC) accounts for 80–85% of lung cancer and can be subdivided into several types based on the type of cells involved [33]. The three main types of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [34]. Lung adenocarcinomas (LUADs) which arise from mucus-secreting gland cells lining the alveoli are the most common type of NSCLC, constituting 40% of lung cancers. Lung squamous cell carcinomas (LSCCs) represent 20% of

lung cancers and originate from squamous cells lining the central bronchi. Approximately 3–10% of all lung cancers are represented by poorly differentiated, pleomorphic, and necrotic large cell carcinomas (LCCs). There are also other rare types of NSCLC, including adenosquamous, pleomorphic, giant cell, and spindle cell carcinomas [19,33].

Treatments for patients with stage I to III NSCLC aim to cure the disease, whereas for stage IV patients, the goal of therapy is to palliate symptoms and prolong survival [35]. The primary treatment for patients with stage I and stage II NSCLC is surgical resection with lobectomy (removal of one lobe of a lung) or pneumonectomy (removal of one of the lungs), along with mediastinal lymph node sampling [35]. Stage II patients may also be treated surgically, followed by adjuvant chemotherapy with cisplatin-based doublet regimen [33]. Concurrent chemoradiotherapy (cCRT) is the first line of treatment for locally advanced, unresectable stage III NSCLC patients. It is superior to sequential chemoradiotherapy (sCRT) by having a significantly higher 5-year survival and response rate of 16% and 70% respectively, compared to that of 10% and 61% respectively in sequential chemoradiation [36]. Platinum-based chemotherapy may be indicated for resectable stage III NSCLC patients pre-operatively (induction chemotherapy) or post-operatively (adjuvant chemotherapy), to increase 5-year survival rate, improve time to distant recurrence and recurrence-free survival, as demonstrated in a few clinical trials [37,38]. Immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab have also been approved by the United States Food and Drug Administration (US FDA) to treat advanced NSCLC patients [39], replacing docetaxel and pemetrexed as the second-line therapy for metastatic NSCLC [40]. Recently, durvalumab, an immunotherapeutic drug which is incorporated in the PACIFIC regimen has also been shown to increase 3-year survival rate (66.3% and 43.5% in the durvalumab and placebo groups, respectively) of unresectable stage III NSCLC patients after CRT, highlighting the long-term survival benefit of this drug [41]. Finally, stage IV patients are normally treated with platinum-based chemotherapy alone, but radiotherapy may also be indicated as a palliative treatment [42]. Advancements in molecular biology also provided new light to the roles of several important cell-signalling pathway in the oncogenesis of NSCLC. This led to the development of targeted therapeutic agents specifically designed to target relevant oncogenic pathways that are aberrated due to genomic alterations in advanced NSCLC, for instance *EGFR*, *KRAS*, and *HER2* driver mutations [35].

2. Treatment landscape of lung cancer

2.1. Chemotherapy

Cisplatin was the first FDA-approved platinum compound for cancer treatment in 1978 [43]. Since then, it has been extensively used in the treatments of various tumours, for instance ovarian cancer, sarcomas, and head and neck cancers. The most common platinum-based chemotherapeutic drugs used in SCLC are cisplatin and carboplatin [44].

Cisplatin is a platinum-based alkylating drug that can cross the cell surface membrane and induce DNA damage in the nucleus. It does so by forming Pt-d(GpG) diadducts which distort the DNA structure and elicits DNA repair or apoptosis [45,46]. In the Lung Adjuvant Cisplatin Evaluation (LACE), cisplatin has been shown to improve OS and disease-free survival (DFS) at an absolute benefit of 5.4% and 5.8% at 5 years, respectively in postoperative NSCLC patients [47]. It is indisputable that platinum-based chemotherapy (cisplatin-etoposide) provides clinically meaningful benefit in lung cancer treatment as this doublet treatment displayed considerably high response rate of up to 80% in ES-SCLC [48]. However, controversies remain in regard to its long-term clinical benefit as a number of evidence has shown that the median OS was only 9–10 months [49,50] and progression-free survival (PFS) of less than 3 months [51].

As cisplatin exerts poor selective cytotoxicity on normal and cancerous cells [52], patients on cisplatin-based treatment often displayed a diverse range of side effects which are dependent on dosage, mode of administration and certain interindividual physiological variations (e.g., age and diet) [53]. One of the most critical side effects of cisplatin is nephrotoxicity; therefore, urinary output should be monitored, and intravenous hydration is mandatory for patients on the treatment course. However, this possesses a risk to patients with congestive heart failure or elderly patients with comorbidities (cardiac and renal failures) [48,54]. Other common side effects include gastrointestinal symptoms (nausea and vomiting) which could be curbed with antiemetic drugs; more detrimental side effects are myelosuppression which warrants close monitoring for infection and haematological toxicity, ototoxicity (hearing loss), neurotoxicity (numbness and paraesthesia), and hepatotoxicity [48,53–55]. Anaemia and leukopenia may arise as a result of myelosuppression since cisplatin indiscriminately exerts its cytotoxic activity to labile cells, in this case, the bone marrow stem cells [52,54]. Additionally, the loss of erythropoietin production due to coexisting renal dysfunction caused by cisplatin may also serve as a mechanism for anaemia [56].

Carboplatin on the other hand is an appealing substitute for cisplatin as it has comparably lesser side effects with myelosuppression. This is because most of the dose-limiting toxicities and nephrotoxicity only develop at a high dosage [52,54]. Evidently, a meta-analysis on twelve randomized trials collected from several databases concluded that in comparison with cisplatin-based combination chemotherapy, carboplatin-based duplet demonstrated lower risk of gastrointestinal and renal toxicities [57]. Although they did report that the treatment was more associated with anaemia and neutropenia [57], but these treatment-associated toxicities were deemed less impactful on a patient's quality of life [58]. Furthermore, there wasn't a significant difference in OS between the two albeit the cisplatin-based chemotherapy yielded slightly better overall response rate (ORR) [57].

Tumour recurrence tend to occur several months after completion of initial platinum-based chemotherapy mainly due to the development of chemoresistance [23]. The four major resistance mechanisms are: reduced cellular uptake of platinum, improved repair mechanism of platinum-induced DNA damage, intracellular deactivation of the drugs, and aberration in apoptosis induction [54]. Reduced intracellular accumulation of cisplatin inherently leads to decreased formation of platinum-DNA adducts and subsequently reduced cytotoxicity [59].

Copper transporter receptor 1 (CTR1) is the primary copper influx transporter in human cells, which also binds to platinum by its methionine-rich clusters in the extracellular domain [60]. The study by Ishida *et. al* provided insight to the role of CTR1 in cisplatin resistance using yeast and murine cells. In their study, yeast cells expressing CTR1-mutant had low intracellular cisplatin concentration and high degree of cisplatin resistance; and CTR1 knockout of mouse embryonic cells led to platinum resistance and reduced cisplatin accumulation [61]. The roles of CTR1 as an independent predictive marker of platinum-based chemotherapy and prognostic factor in NSCLC also came to light in a previous study by a group of Taiwanese researchers. Their study reported that patients with low levels of CTR1 had bad prognosis (PFS and OS of 5.3 and 14.9 months respectively) when treated with platinum-based doublet regimen [62]. Since then, several studies have found a link between genetic polymorphisms of CTR1 with platinum resistance and prognosis, as well as tolerability to platinum toxicity [63]. In another study to interrogate the relationship between CTR1 expression and tumour platinum concentration in clinical specimens, it was demonstrated that NSCLC tumour samples with undetectable CTR1 expression (IHC staining score of 0) had significantly lower platinum concentration and tumour response to platinum drug compared with other tumours with an IHC staining score of 1+ or above [64].

On the contrary, copper transporter receptor 2 (CTR2) serves as a copper and platinum efflux transporter despite having a highly similar structural homology as CTR1 [60]. Evidently, decreased CTR2 expression in mouse embryo fibroblasts was shown to increase cisplatin

accumulation and enhance sensitivity of cells to cisplatin-induced cytotoxicity [65]. Another study also demonstrated similar findings using human epithelial 2008 cancer cells, whereby an approximately 50% reduction of CTR2 mRNA expression was able to enhance cisplatin sensitivity to up to 2.9-fold, whereas the cells with overexpressing CTR2 were 2.5-fold more resistant than control cells [66]. CTR2 has been shown to regulate CTR1 function by cooperating with cathepsins L and B to induce ectodomain cleavage of full-length CTR1 into a truncated form of CTR1 [67]. This truncated CTR1 is less efficient in copper and platinum import, hence causing decreased drug accumulation [68,69].

Increased drug export can also contribute to reduced intracellular drug accumulation. ATP7A and ATP7B are copper-exporting P-type adenosine triphosphatases (ATPases) which have also been shown to mediate platinum efflux [60]. ATP7A is localized in cytoplasmic vesicle membrane and trans-Golgi network and sequesters platinum. An *in vitro* study using resected NSCLC tumours showed an inverse correlation between ATP7A expressions and chemosensitivity [70]. In their study, ATP7A expression was higher in chemoresistant NSCLC cells compared to the parental cells; silencing of ATP7A was shown to reverse platinum drug resistance [70]. In another study, ATP7A was also overexpressed in the chemoresistant NSCLC patients and was associated with poor chemotherapy response rate and OS [71]. Likewise, ATP7B which is a structural homolog of ATP7A [72], was also associated with increased resistance to platinum drugs [73]. Song *et. al* improvised the conventional liposomal drug delivery system by incorporating OMI-CDDP-N into liposome to effectively deliver cisplatin to resistant cells [74]. OMI-CDDP-N-based liposome (OCP-L) has been shown to successfully inhibit ATP7B function and reverse the drug resistance in lung cancer cells [74]. Furthermore, the functional OMI can also increase the permeability of cell surface membrane leading to increased cellular uptake of drug and enhance platinum-induced cytotoxicity due to its labile monocarboxylato and O→Pt coordinate bond [74].

Cisplatin has high affinity for the cysteine-rich proteins glutathione (GSH) and metallothionein (MT) [75]. GSH is an electrophile scavenger that protects the cell from oxidative damage which is critical for cell survival [76]. Several roles of GSH in governing cisplatin resistance have been proposed: GSH facilitates cisplatin drug efflux by cooperating with multidrug resistance proteins (MRP1 and MRP2) and acts as a cytoprotector by coupling with glutathione disulfide (GSSG) in the redox cycle to neutralize cisplatin-induced oxidative stress [77]. Culturing the cells with exogenous GSH was shown to induce cisplatin resistance in NSCLC cells by upregulating the expressions of glutathione S-transferase pi (GST-π) which mediates the formation of GSH-platinum conjugates to facilitate cisplatin excretion [75]. Other than that, introduction of GSH in NSCLC cells also caused cisplatin resistance due to upregulation of gamma-glutamylcysteine synthetase (γ-GCS) involved in GSH biogenesis; the efflux pump MRP1; and B-cell lymphoma 2 (Bcl-2) expression which was accompanied by downregulation of proapoptotic bax and caspases [76].

Increased DNA damage repair and inactivation of cell apoptosis are also important factors in the development of chemoresistance [75]. A study found out that in cisplatin-resistant NSCLC cells, the protein levels of some major relevant genes involved in cell cycle regulation and apoptosis including *p53*, ataxia telangiectasia mutated (*ATM*), murine double minute 2 (*MDM2*), and *p21* were significantly lower than normal cisplatin-sensitive cells upon treatment [78]. Moreover, other proapoptotic genes were also lowly expressed in resistant cells, resulting in abrogated G2/M cell cycle arrest and lower apoptosis level [78]. These genes were xeroderma pigmentosum complementation group C (*XPC*), a downstream effector of p53 pathway involved in DNA damage recognition [79]; stress-induced protein (*SIP*), also known as tumour protein p53 inducible nuclear protein 1 (*TP53inp1*) which is a p53 cofactor essential for transcriptional activation of p53 target genes involved in apoptosis [80]; and growth arrest and DNA damage-inducible protein 45 alpha (*GADD45*α) which regulates cell cycle progression and DNA damage repair [81]. Endonuclease excision repair cross-complementation group 1 (ERCC1) is a nucleotide excision repair (NER)-associated protein that has long been implicated in cisplatin resistance across several cancer types [75]. A recent study reported that ERCC1 was highly expressed in 47.3% of LUAD patients who received platinum-based chemotherapy and was associated with higher TNM, lymph node involvement and metastasis [82]. Conversely, patients with low ERCC1 expression had longer OS regardless of cancer stages when treated with platinum drug alone or in combination with surgical resection or radiotherapy [82].

As cisplatin resistance impedes its clinical application for cancer treatment, emerging studies focusing on methods to counteract it therefore become more important to this group of resistant patients. In a study, it was demonstrated that metformin was able to circumvent cisplatin resistance in NSCLC cells potentially by inhibiting the mammalian target of rapamycin (mTOR) pathway that was overactivated in cisplatin-resistant cells. Metformin was shown to do so by downregulating the expression of oncogenic protein annexin 4 (ANXA4) [83], which is often upregulated in cisplatin-resistant lung cancer cells [84] and acts upstream of AKT [85]; and by upregulating the antioxidant enzyme superoxide dismutase 2 (SOD2) [83]. Additionally, previous studies have also indicated that metformin can inhibit the mTOR pathway by mediating the AMPK signalling in various cancers [86,87], suggesting that the inhibition of mTOR signalling is a key mechanism in the antitumour activity demonstrated by metformin [88]. Cordycepin is a traditional herbal medicine widely incorporated in cancer treatment in traditional Chinese Medicine. Interestingly, it has been found to not only act synergistically with cisplatin in inhibiting NSCLC cell growth, but also reversed cisplatin resistance by downregulating GSH, activating the AMPK pathway, and inhibiting the AKT/mTOR signalling [89]. A study reported an intriguing finding in which, genetic mutations in the *GREB1* gene may contribute to primary resistance to cisplatin by aberrating the four mechanisms in chemoresistance (reduced cellular uptake, enhanced DNA damage repair, detoxification of drug, and increased oncogenic signalling) [90]. Hence, this study suggested that *GREB1* may serve as a gene mutation biomarker in cisplatin resistant LUAD patients [90]. Figs. 1–8.

2.2. Immunotherapy

Immune checkpoints are key regulators of the immune system that control the balance between co-stimulatory and inhibitory signals, which are important for self-tolerance as well as in initiating a protective response against pathogens [91]. Programmed cell death protein 1 (PD-1) is expressed on activated T-cells as well as in tumour-infiltrating lymphocytes (TILs) in different tumours [91]. PD-L1 and PD-L2 (CD273 and B7-DC) are the two ligands for PD1 [91]. PD-L1 (CD274 and B7-H1) is broadly expressed on antigen presenting cells, macrophages, B and T cells [92], whereas PD-L2 is expressed primarily on dendritic cells and macrophages [39]. Under normal physiologic condition, the binding of PD-L1 or PD-L2 to PD-1 on the activated T-cells lead to its inactivation by inhibiting interleukin 2 (IL-2) synthesis and T cell receptor activity [93]. In tumour cells, the constitutive activation of oncogenic signalling pathways, to name a few, the PI3K/AKT, MAPK, JAK-STAT, NFκB, and WNT signalling pathways leads to PD-L1 upregulation on their cell surface, which ultimately results in abrogated antitumour immune response of lymphocytes [91,92].

The PD-1/PD-L1/2 pathway therefore serves as an attractive target to be exploited in the development of cancer immunotherapeutic agents. Immune checkpoint inhibitor (ICI), as its name suggests, exerts antitumour activity by blocking the PD1/PD-L1/2 pathway to enhance intratumoural immune response [91]. Nivolumab is a fully human IgG4 monoclonal antibody and a PD-1 inhibitor that has received US FDA approval as a second-line treatment for NSCLC [39,94]. The CheckMate 017 trial was the pivotal randomized trial that earned nivolumab an approval from US FDA in 2015 [95]. In the trial, NSCLC patients who received nivolumab demonstrated superior survival outcomes to

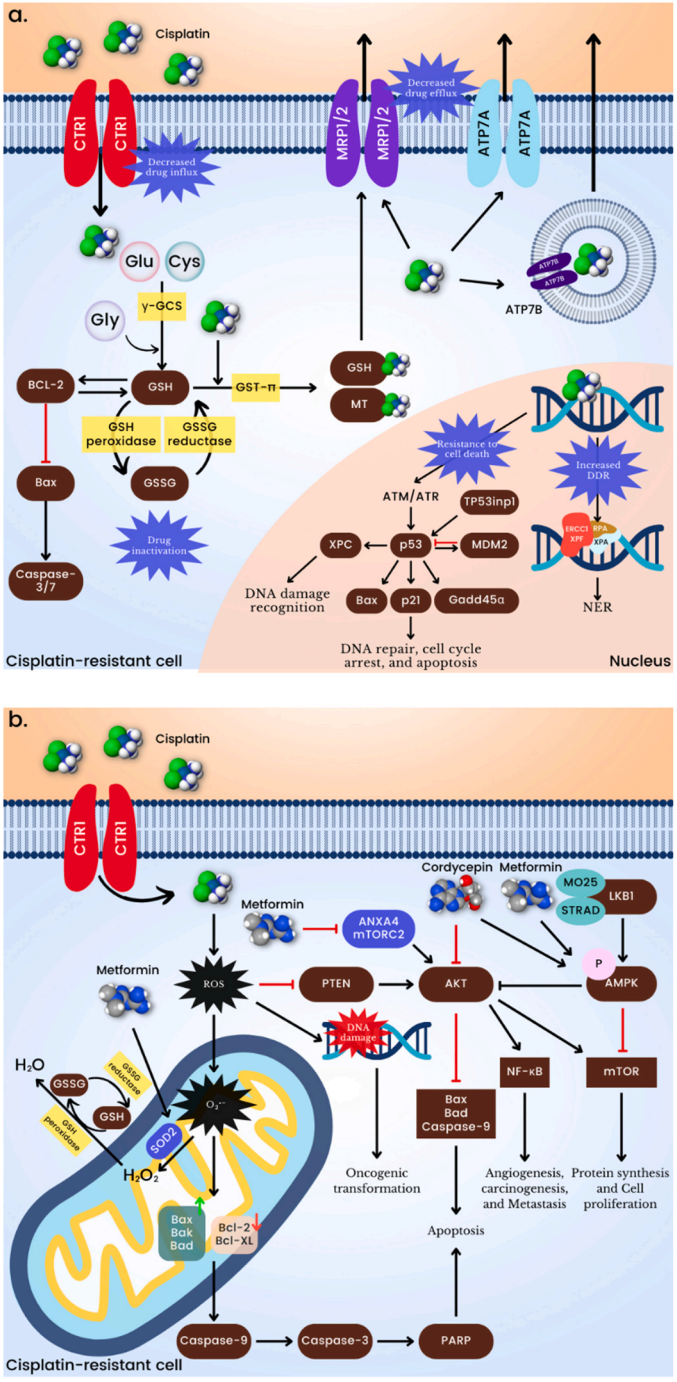

Fig. 1. Mechanisms of cisplatin resistance in cancer cell. (a) The major mechanisms involved in the emergence of cisplatin resistance are decreased drug uptake, increased drug export, increased detoxification of drugs, enhanced DNA damage repair, and supressed cisplatin-induced apoptosis. (b) Possible mechanisms of metformin and cordycepin in the resensitization of cancer cell to cisplatin. Metformin increases SOD2 expression which protects cancer cell from oxidative damage by scavenging mitochondrial superoxide; and decreases ANXA4 expression which suppressed the AKT pathway activation. Inhibition of the mTOR pathway is mediated by metformin and cordycepin by inhibiting and activating the AKT and AMPK signalling, respectively.

docetaxel, with an OS of 9.2 months compared to that of 6.9 months in docetaxel group, and 41% lower risk of death [96]. In the CheckMate 816 trial published more recently, nivolumab when given as a neoadjuvant treatment with chemotherapy to resectable NSCLC patients resulted in markedly longer event-free survival (EFS) than the group treated with chemotherapy alone (31.6 months vs 20.8 months), and higher pathological complete response (24% vs 2.2%) [97]. Additionally, there was no significant difference in grade 3 or 4 treatment-related adverse events in the nivolumab plus chemotherapy group and the chemotherapy alone group (33.5% vs 36.9%) [97]. The most common serious adverse events were neutropenia and decreased neutrophil count which occurred in 8.5% and 7.4% of the patients treated with nivolumab plus chemotherapy [97]. Based on these results, the US FDA granted the approval for nivolumab combined with platinum-doublet chemotherapy as the first neoadjuvant therapy for early-stage NSCLC as of March 4, 2022. As with nivolumab, pembrolizumab was also approved by US FDA on the same year but was only approved for the treatment in PD-L1 positive NSCLC patients or those who show disease progression after platinum-based chemotherapy [98]. The approval was based on the KEYNOTE-010 trial that showed pembrolizumab was able to produce an ORR of 41% and a more acceptable toxicity profile than docetaxel in postoperative PD-L1 expressing advanced NSCLC patients [95,99].

Even though the clinical benefits of immunotherapy have been well demonstrated in ample of evidence, most patients with NSCLC failed to respond at all or only responded partially to ICI treatments due to primary or innate resistance [100]. Meanwhile, another group of patients may respond well to initial treatment but will eventually develop resistance (secondary or acquired resistance) [100]. Undoubtedly, innate and acquired immunotherapy resistance present a profound challenge for that they limit the utility of ICIs in lung cancer treatment. Intrinsic resistance which arises in relation to the inherent genomic profile of the cancer cell includes low immunogenicity (low non-synonymous TMB score), concurrent alterations in oncogenes and tumour suppressor genes (which alter intracellular signalling pathways and immune response), and epigenetic alterations on immune response-related genes. Other than that, factors affecting antigen presentation may also confer intrinsic resistance. For instance, loss of neoantigen load by immunoediting and inflammatory cytokine production, and defects in the important components of antigen processing and presentation such as transporter associated with antigen processing (TAP), β2-microglobulin (B2M), major histocompatibility complex class 1 (MHC-1), and T-cell receptor also play a part in the emergence of intrinsic resistance by compromising antigen presentation [100,101]. Extrinsic mechanisms include the relative density of antitumouric immune cells (CD8+ T-cells and M1 macrophages) and immunosuppressive cells (T-regs, M2 macrophages, and myeloid-derived suppressor cells), high levels of immunosuppressive cytokines (TGF-β, TNF-α, and VEGF), compromised antigen presentation and T-cell priming, activation of co-inhibitory receptors other than PD-1 (LAG-3, TIM-3, TIGIT, and VISTA) and T-cell exhaustion owing to upregulation of PD-1 and epigenetic regulation [100,101]. Host-related mechanisms such as gut microbiome (cross-reactivity of microbial with tumour antigens and altering immune response), diet (affects gut microbiome composition and immune function), long-term steroidal drug use [100] also contribute to ICI resistance.

In the present day, there is extensive research focusing on the development of novel treatment regimen to overcome immunotherapy resistance by targeting each of the underlying mechanism. For instance, the CITYSCAPE trial reported that the combination treatment of atezolizumab (PD-L1 inhibitor) and tiragolumab (TIGIT inhibitor) improved median OS (23.2 vs 14.5 months) and PFS (5.6 vs 3.9 months) when compared with atezolizumab treatment alone in PD-L1 positive NSCLC patients [102]. 21% of patients receiving the combination treatment experienced similar serious treatment-related adverse events as those received atezolizumab plus placebo, and the most reported grade 3 or worse treatment-related adverse event was an increase in lipase levels, observed in 9% of patients [102]. Overall, these results suggest that the atezolizumab plus tiragolumab combination therapy is clinically beneficial with a good safety profile [102]. Other than that, in the Impower010 randomised phase III trial, the combination of atezolizumab with cisplatin-based chemotherapy also showed DFS benefit with a

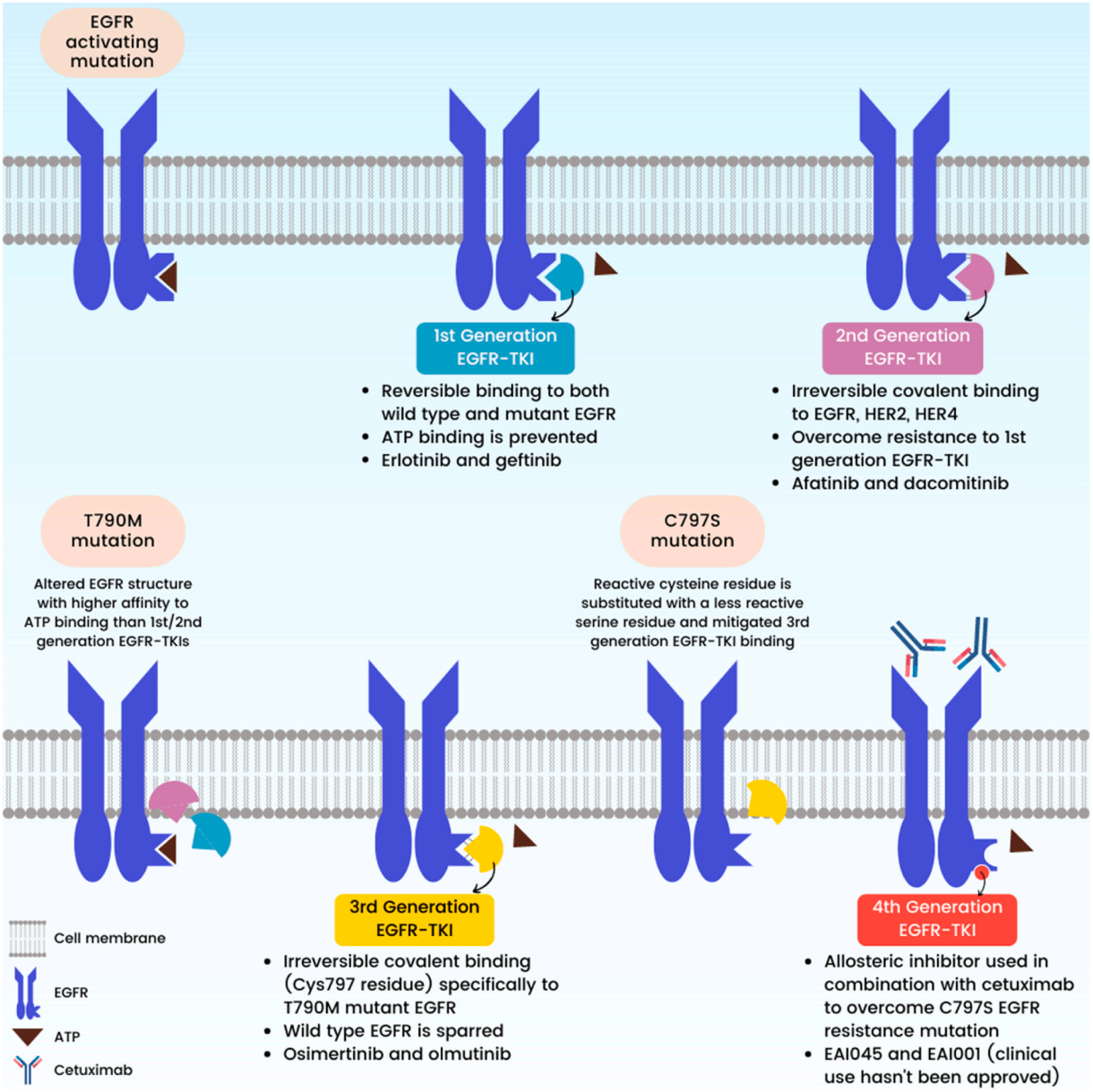

Fig. 2. Mechanisms of acquired resistance to EGFR-TKIs. The emergence of resistance to first- and second-generation EGFR-TKIs is due to T790M gatekeeper mutation, which leads to increased affinity to ATP binding. Acquired tertiary EGFR resistance due to a point mutation at the cysteine residue 797 of EGFR confers drug resistance to third-generation EGFR TKIs.

hazard ratio of 0.66 in patients expressing PD-L1 in 1% or more of tumour cells [103]. This synergy was achieved possibly because the chemotherapeutic agents could increase neoantigen load by inducing cell death, upregulating MHC-1 expression, and regulate the composition of immune cells in tumour microenvironment (TME) [100,101]. Other resistance mechanisms such as oncogenic signalling pathway activation, epigenetic factors, and factors affecting antigen presentation and TME which ultimately influence immune response, also serve as attractive targets of therapeutic strategies on the mission to vanquish immunotherapy resistance [100].

2.3. Radiotherapy

Radiotherapy is an important treatment modality in cancer management, as it has been indicated in half of all patients in all stages of lung cancer for curative and palliative treatments [104,105]. Generally, the efficacy of radiotherapy in cancer treatment is dependent on the 4 R's of radiobiological principle: repair of DNA damage by NHEJ, redistribution of cells in different phases of cell cycle which show differential radiosensitivity, repopulation of cells after radiation, and reoxygenation of surviving cancer cells in hypoxic regions which could increase tumour radiosensitivity [106,107].

External beam radiotherapy (EBRT) is a conventional radiotherapy that is usually delivered in small-dose fractions of 2 Gy per day, 5 days a week over a period of 4–6 weeks [107]. Reoxygenation and redistribution lead to radiosensensitization of tumour cells and offer therapeutic advantages in EBRT [107]. Oxygen molecule (O_2) is a critical element in radiation treatment as it is required for the generation of highly reactive free radicals that can induce DNA damage. Therefore, it could be said that hypoxic cells are generally more resistant to radiation compared with cells that are well oxygenated [107]. Since EBRT is delivered in multiple fractions, the tumour cells in hypoxic areas can reoxygenate in the time between each fraction and become more sensitive to radiation. In general, tumour cells in the G2/M stage are the most susceptible to

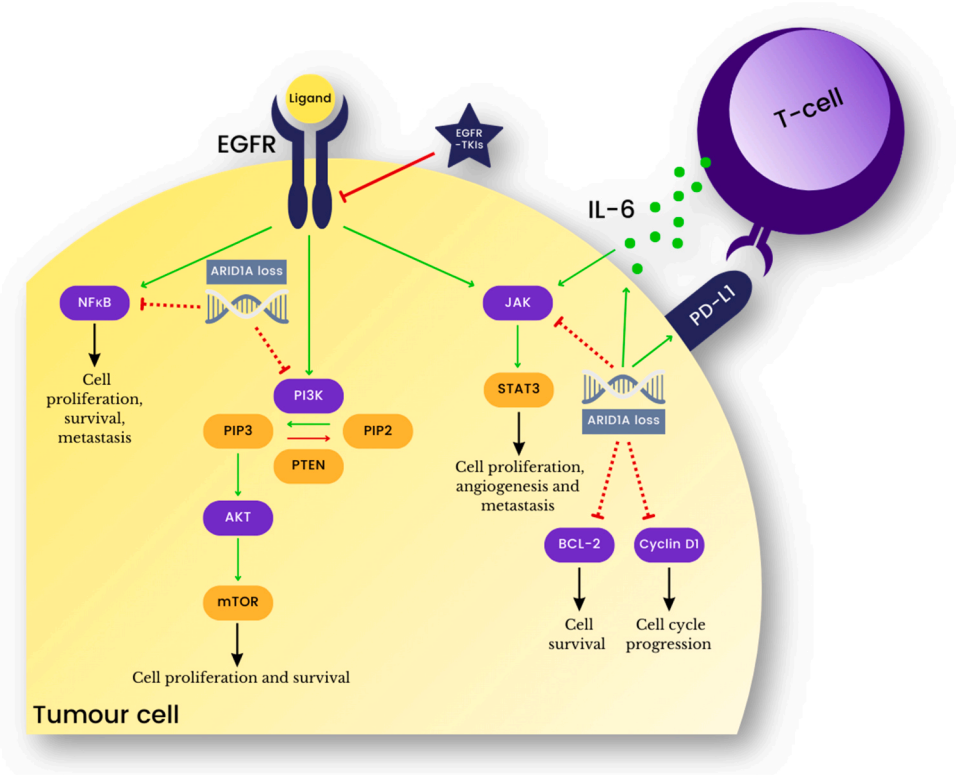

Fig. 3. Implication of ARID1A alterations in the development of lung cancer. LOF mutations of ARID1A confer EGFR-TKI resistance in NSCLC due to reduced inhibition on the downstream pathways of EGFR, the PI3K/AKT, NFκB, and JAK/STAT signalling pathways. ARID1A downregulation also leads to upregulation of antiapoptotic BCL-2 gene expression and cyclin D1 protein expression, which results in increased cell cycle progression, cell survival and proliferation. However, ARID1A loss is also associated with increased ICI clinical efficacy in NSCLC patients due to enhanced PD-L1 expression via PI3K/AKT pathway activation; increased proinflammatory IL-6 production which stimulates tumour immunity and activates the JAK/STAT3 pathway; and increased TMB due to impaired DNA damage repair.

radiation, whereas cells in the S phase are the most resistant [106]. In multi-fractionated EBRT, the cells from the S phase are given time to reassort themselves into radiosensitive G2/M phase of the mitotic cell cycle [107]. This therefore enhances the efficiency of radiation-induced cell death [107]. On the other hand, normal cells which are normally accumulated at the quiescent (G0/G1) phase also progress slowly within the cell cycle, can therefore be spared from radiation [106,108]. As EBRT is delivered in low doses in multiple fractions over a long period of time, there is a tendency for the tumour cells to become radioresistant due to sublethal DNA damage which allows subsequent DNA repair [107]. Other than that, tumour cells also tend to exploit the duration between radiation fraction of EBRT to repopulate, which certainly will counteract the cell killing effect of radiation treatment [107].

Over the years, the accelerated improvements in technology have driven the emergence of some advances in radiation treatment modalities. To mention a few, those include three-dimensional-conformal RT (3D-CRT), intensity modulated radiotherapy (IMRT), volumetric intensity modulated arc therapy (VMAT), and stereotactic body RT (SBRT) [109]. The incorporation of image-guidance tools such as magnetic resonance imaging (MRI), positron emission tomography (PET), along with computer tomography (CT) scans allowed accurate tumour localisation prior to treatment for effective radiation delivery while minimizing damage to normal surrounding tissues [110]. On the other hand, image-guided radiotherapy (IGRT) using cone beam CT (CBCT) is widely used to correct interfractional motions (daily variations in target tumour position) and tumour localisation during treatment planning [111]. Four-dimensional computed tomography (4D-CT) is superior to CBCT in that it can eliminate tumour motion artefacts in CT images caused by respiration during the radiotherapy session (intrafraction motions) [110,111].

Stereotactic ablative body radiotherapy (SABR) is the standard of care for the treatment of inoperable stage I NSCLC patients [112]. It is used to deliver large (ablative) doses of radiation in small fractions to a defined volume of tumour while sparing adjacent normal tissues [109]. It has been demonstrated to have a high primary tumour control rate of over 90%, and 5-year survival rates of over 50% in patients with stage I NSCLC [113,114]. The SPACE trial has reported reduced toxicity (esophagitis and pneumonitis) and significantly improved quality of life with SABR treatment (66 Gy delivered in 3 fractions) compared to the conventional 3DCRT (70 Gy delivered in 35 fractions), although there was no difference in PFS and OS [115]. The superiority of SABR to standard radiotherapy in the treatment of inoperable stage I NSCLC has also been demonstrated in the CHISEL trial, where it has been shown to improve OS and better local tumour control with minimal toxicity [116]. One of the advantages of SABR is that it requires only one to five treatments over a period of one to two weeks, and this is particularly appealing for the treatment of stage I NSCLC in elderly patients [116,117]. It provides a potential curative treatment for elderly patients with stage I NSCLC who otherwise would be left untreated due to patient's refusal, comorbidity, and high operative risks for surgical resection [117].

2.4. Targeted therapy

Targeted therapy is indicated for advanced NSCLC with specific genomic alterations. To date, the FDA approved oral drugs for targeted therapy for advanced NSCLC are erlotinib, gefitinib, afatinib, and osimertinib which are tyrosine kinase inhibitors (TKIs) used to target intracellular domain of epidermal growth factor receptor (EGFR); crizotinib, ceritinib, alectinib, and brigatinib which are indicated for

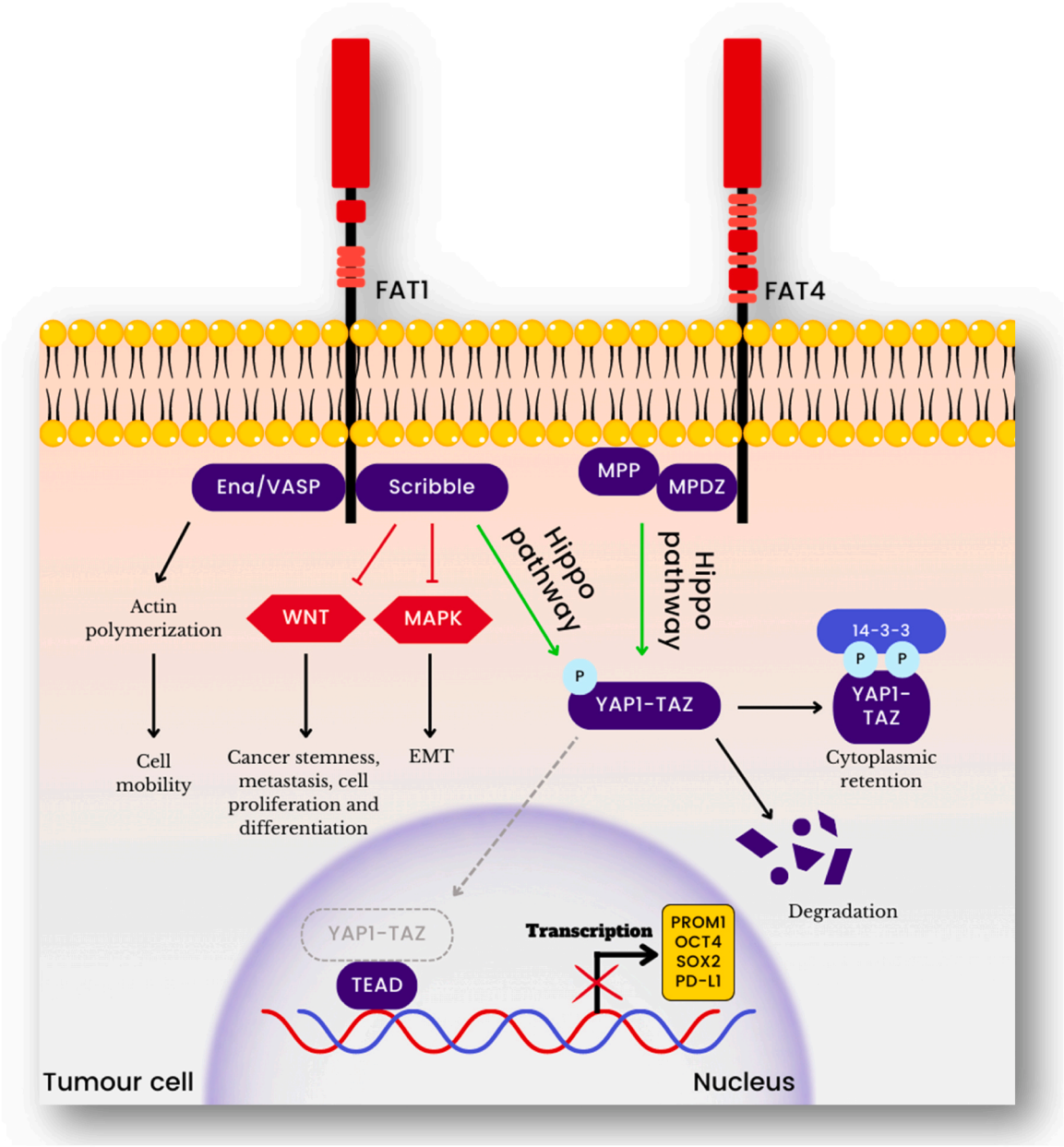

Fig. 4. Functions of FAT family protein in cancer development. FAT1 has dual role as an oncogene and a tumour suppressor gene in cancers. It promotes cell mobility at the lamellipodia and filopodia (cytoskeletal and cytoplasmic extensions on the leading edge of migrating cells) by interacting with Ena/VASP and Scribble proteins. Conversely, it also induces YAP1 phosphorylation via the Hippo pathway and leads to cytoplasmic retention or proteolytic degradation of YAP/TAZ. In cancers, aberrant activation of YAP1/TAZ and its nuclear translocation activate the transcription of its target genes essential for cell survival, EMT, and metastasis. The loss of FAT1 function also causes overactivation of MAPK/ERK and WNT pathways resulting in EMT and cancer stemness. FAT4 is crucial for planar cell polarity (PCP) in epithelial tissue by interacting with MPDZ to recruit MPP5. Its function is fundamentally tumour suppressive in which it inhibits cell growth via the Hippo pathway.

NSCLC patients with anaplastic lymphoma kinase (*ALK*) mutations; and sotorasib as a Kristen rat sarcoma virus (KRAS) G12C inhibitor. There are also other therapeutic drugs that have been approved or currently in ongoing clinical trials that specifically target some of the less common genetic alterations in NSCLC patients, such as *ROS1, MEK*, *MET*, *BRAF*, *HER2*, *RET* mutations [118]. According to the COSMIC database, EGFR, ALK, and KRAS are the top 3 oncogenes among the list of most commonly mutated genes in NSCLC patients [119].

2.4.1. *EGFR*

Epidermal growth receptor (*EGFR*) gene located on chromosome 7p11.2 is constituted by 28 exons encoding the EGFR transmembrane glycoprotein, that is also known as erbB1 (HER1) [120]. It belongs to the erbB family which consists of other closely related tyrosine kinases, such as erbB2 (HER2), erbB3 (HER3), and erbB4 (HER4) [121]. The EGFR protein is composed of a ligand-binding extracellular domain, a transmembrane sequence, an intracellular tyrosine kinase domain with catalytic activity, and a C-terminal regulatory segment with several phosphorylation sites [122,123]. The EGFR kinase domain is made up of an N-lobe which comprises of five β strands and the αC helix; and a C-lobe which is composed of five α helices along with an activation loop (A-loop) [124]. In between the N-lobe and C-lobe is the adenosine triphosphate (ATP)-binding site which is found underneath the glycine-rich phosphate-binding loop (P-loop) that can interact with and anchor the phosphates of ATP by forming hydrogen bonds with its backbone amides [125].

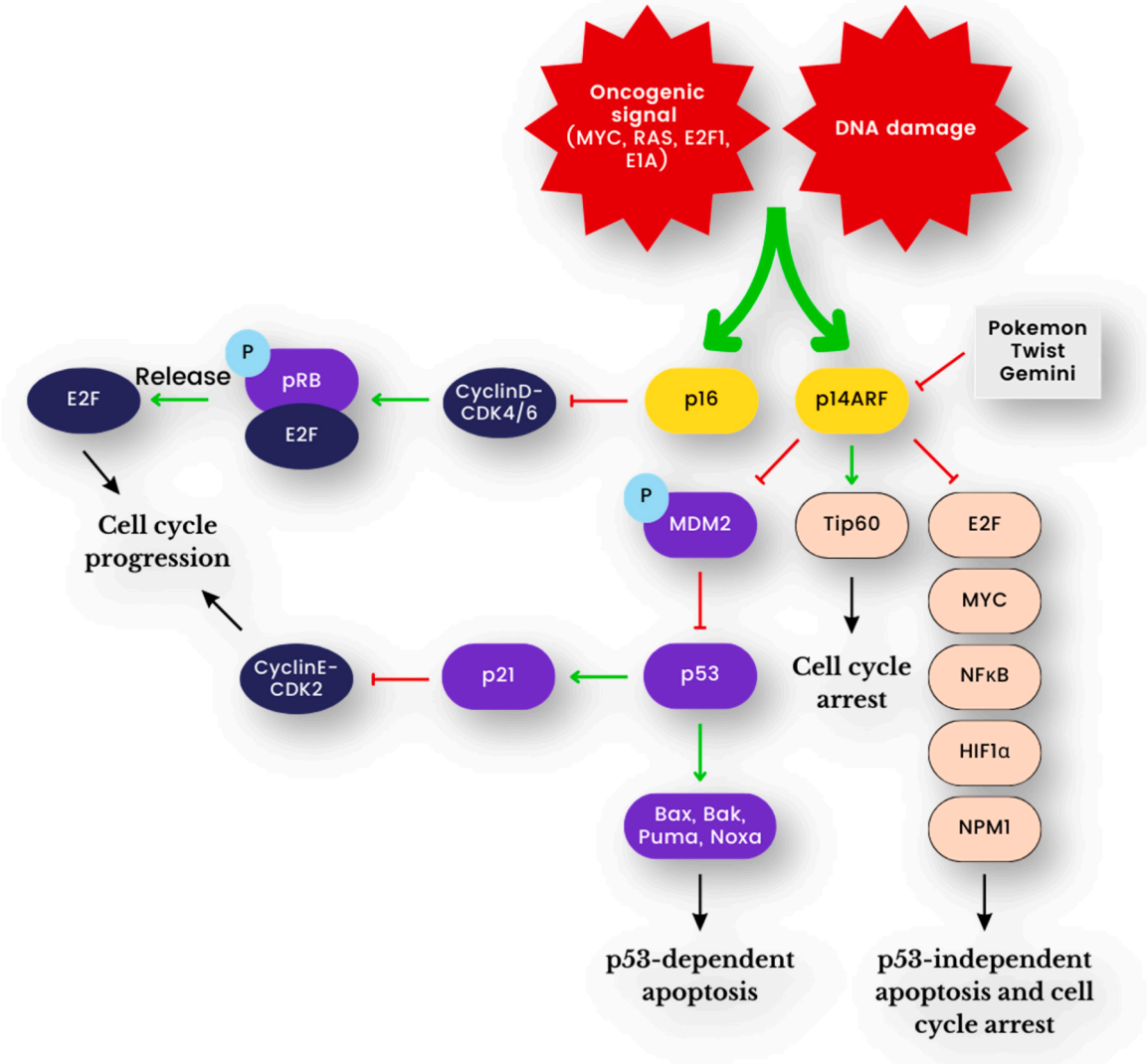

Fig. 5. The roles of p14ARF and p16 signalling in lung cancer. p16 inhibits G1/S cell cycle progression by inhibiting cyclin D-CDK4/6 complex and maintains RB protein in its hypophosphorylated state. CDKN2A gene also generates the splicing variant $p14^{ARF}$ which encodes the P14ARF which is functionally distinct from p16. P14ARF can induce both p53-dependent and independent tumour suppressive effects. Inhibition of MDM2 by p14ARF protects p53 from proteolytic degradation (and inhibition) which subsequently leads to apoptosis; and activates the CDK inhibitor p21 to induce cell cycle arrest. The p53-independent pathway of cell growth inhibition involves the downregulation of E2F, c-Myc, NFκB and HIF1α transcription factors. p14ARF also interacts with Tip60, NPM1 and other nucleolar proteins to inhibit cell proliferation.

EGFRs exist as monomers in the cell membrane. Upon ligand (e.g., epidermal growth factor) binding, the EGFR molecules dimerize and bring the two neighbouring kinase domains in close proximity. The stimulated kinase in the EGFR leads to trans-autophosphorylation of the tyrosine residues in the C-terminal segments, which now serve as the docking sites for adaptor molecules such as growth factor receptor-bound protein 2 (GRB-2), Src homology and collagen (SHC), and Son of sevenless homolog (SOS) [126,127]. Activated EGFR ultimately leads to activation of its downstream pro-survival signal pathways (PI3K/AKT/mTOR, ERK/MAPK, and JAK-STAT pathways), contributing to cell proliferation, adhesion, and reduced apoptosis [120].

EGFR mutations typically occur between exons 18–21, which are predominated by deletion mutations (44%) on exon 19, followed by point mutation (41%) on exon 21 (L858R). Other rare missense mutations across the 4 exons, insertion mutations on exon 20 and point mutation on exon 18 (G719X) account for a small proportion of the *EGFR* mutations (15% in total) [128]. Exons 18 and 19 encode the phosphate-binding loop (P-loop), whereas exons 20 and 21 encode the αC helix and activation loop (A-loop) of the kinase domain, respectively [121]. Thus, L858R or L861Q (or L837Q in mature EGFR) mutations affecting the A-loop could disrupt the conformational structure and autoinhibitory interaction of the inactive kinase domain, hence leading to constitutive activation of EGFR kinase [122,129]. Besides, exon 19 deletions occurring between the β3-αC loop at the N-terminus of the kinase domain, and exon 20 insertions in the αC-β4 loop and C-terminus of the αC-helix are also thought to increase basal activity of the kinase domain [122]. *EGFR* mutations frequently occur in NSCLC and has an association with female gender, Asian origin, adenocarcinomas, and cigarette smoking. In LUAD, *EGFR* mutations affect 10–15% of the Caucasian patients and in comparison, the mutations are more and highly prevalent in the Asian patients, accounting for over 50% of the cases [130–133].

Erlotinib and gefitinib are the first-generation EGFR TKIs that can bind reversibly to ATP-binding site of EGFR [134]. EGFR-mutant LUAD patients who are initially treated with first-generation TKIs may show superior therapeutic outcomes compared to conventional chemotherapy, but will eventually develop acquired resistance 10–16 months into treatment [135]. Afatinib and dacomitinib are second-generation

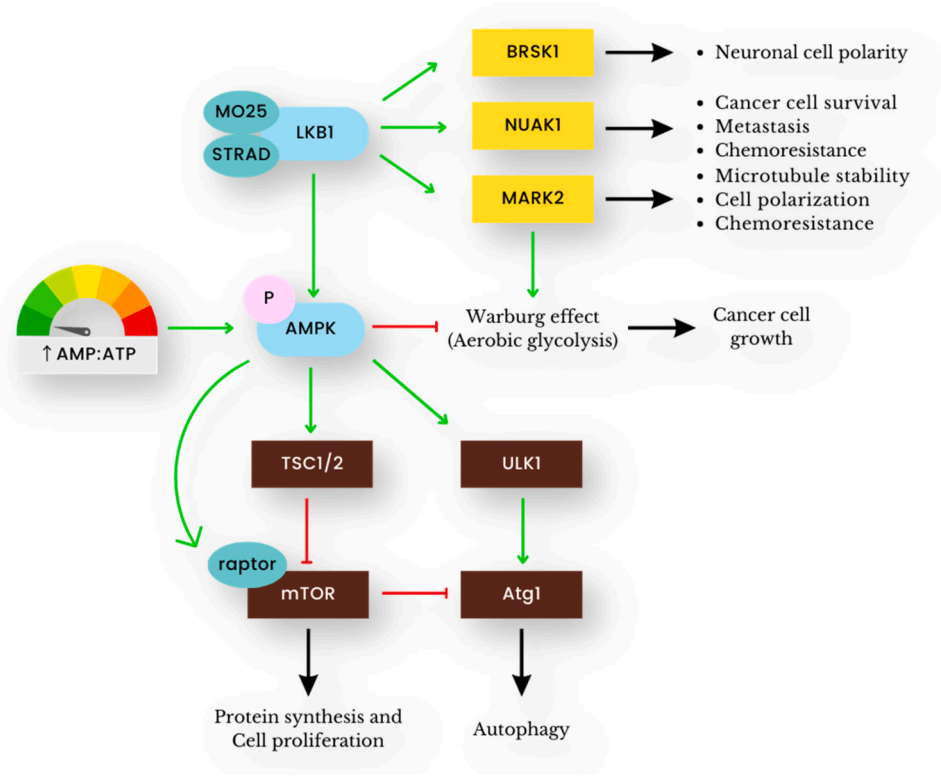

Fig. 6. Implication of the LKB1/AMPK pathway in cancers. The downstream effectors of LKB1 such as AMPK, BRSK1, NUAK1, and MARK2 are involved in the regulation of cell growth, polarity, motility and energy metabolism. In lung cancer, LKB1 also paradoxically interactsi with other AMPK-related kinases (ARKs), such as NUAK1 and MARK2 with oncogenic roles in which they induce lung cancer cell proliferation, tumour invasion and confer resistance to chemotherapy.

TKIs that are used to overcome the resistance to first-generation TKIs by irreversibly binding to Cys797 residue of the kinase domain of the ErbB receptors including EGFR (HER1) and HER2, and HER4 [134]. However, due to their non-selectivity inhibition on both the mutant and wild-type EGFR, majority of the patients will commonly suffer from skin (rash) and gastrointestinal (diarrhea) toxicities [134,136].

Several lines of evidence indicated that T790M gatekeeper mutations occur in over half of the patients who developed acquired resistance, whereby the mutations increase the affinity of tyrosine kinase domain to ATP binding, rendering both the first- and second-generation TKIs inactive [135,137,138]. Other alternative mechanisms for acquiring resistance to standard TKIs may include aberrations of other bypass track such as hyperactivation of MET/PI3K/AKT pathway and *PTEN* deletion leading to upregulation of PI3K/AKT pathway; and morphological alterations of cancer cells (SCLC transformation and epithelial-mesenchymal transition; EMT) [139]. Notably, MET proto-oncogene, receptor tyrosine kinase (*MET*) amplification also occurred in approximately 20% of the gefitinib-resistant cases, which caused constitutive activation of the ERBB3/PI3K/AKT signalling [140,141]. *MET* gene encodes the transmembrane receptor tyrosine kinase c-MET, which is activated upon the binding of its ligand, hepatocyte growth factor (HGF). Activation of MET receptor subsequently leads to activation of its downstream signalling pathways including PI3K/AKT, STAT3, RAS/MAPK, and Wnt/β-catenin that drive cell growth, survival, and migration [142].

Hence, a third generation TKI, osimertinib (AZD9291) developed by AstraZeneca was approved by the US FDA in 2015 as the first-line treatment for patients with mutant EGFR-T790M NSCLC [136]. The AURA phase I and III trials have proven the safety and clinical benefits of osimertinib treatment for EGFR-mutant patients with T790M mutation [143–145]. Particularly, in the phase III AURA trial, osimertinib displayed significantly better ORR and PFS, as well as lesser adverse events compared to platinum-pemetrexed chemotherapy [145]. On the other hand, the FLAURA trials were conducted to compare the efficacy of osimertinib to the first-generation TKIs (erlotinib and geftinib) in advanced NSCLC patients with untreated EGFR mutations. In the double-blinded phase III FLAURA trial, osimertinib was shown to improve PFS better than the standard TKIs (18.9 months compared to 10.2 months), and lower rate of adverse events [146]. Osimertinib also demonstrated superior clinical efficacy to the first-generation TKIs in terms of improving OS in another FLAURA trial reported in 2020, by having a median OS of 38.6 months compared to 31.8 months in the group treated with geftinib or erlotinib [147]. In the osimertinib group, the only serious adverse events were stomatitis and renal symptoms each reporting only one patient, and the most commonly reported adverse events were milder symptoms such as diarrhoea, rashes, and dry skin [147]. Other third-generation TKIs, such as olmutinib (HM61713) and lazertinib (YH25448) were also approved for use in South Korea in recent years to treat EGFR T790M-positive advanced NSCLC patients [148,149].

Third generation TKIs selectively inhibit the EGFR-mutants by irreversibly binding to the ATP-binding site and by forming covalent bond to Cys797 residue of the kinase domain, while sparing the wild-type EGFR [150–152]. However, acquired resistance to osimertinib may also inevitably develop as a result of a tertiary *EGFR* mutation (C797S) [153], or less commonly, EGFR-independent mechanisms such as *MET* and *HER2* amplifications, *CDK4/6* copy number gain, *RET* fusions, or genetic alterations in *PIK3CA*, *BRAF*, or *ALK* [139,152,154]. Mutation at the *EGFR* C797 codon attenuates covalent binding of the third generation TKIs to the EGFR ATP-binding site since the reactive cysteine residue has been substituted with a less reactive serine residue [136]. To date, the development of fourth-generation EGFR TKIs to target the C797S mutation is still underway. EAI045 was discovered as the first EGFR allosteric inhibitor that can overcome L858R/T790M mutations when used in combination with cetuximab in EGFR-mutant NSCLC [136,155]. Interestingly, a study discovered that amplification of the

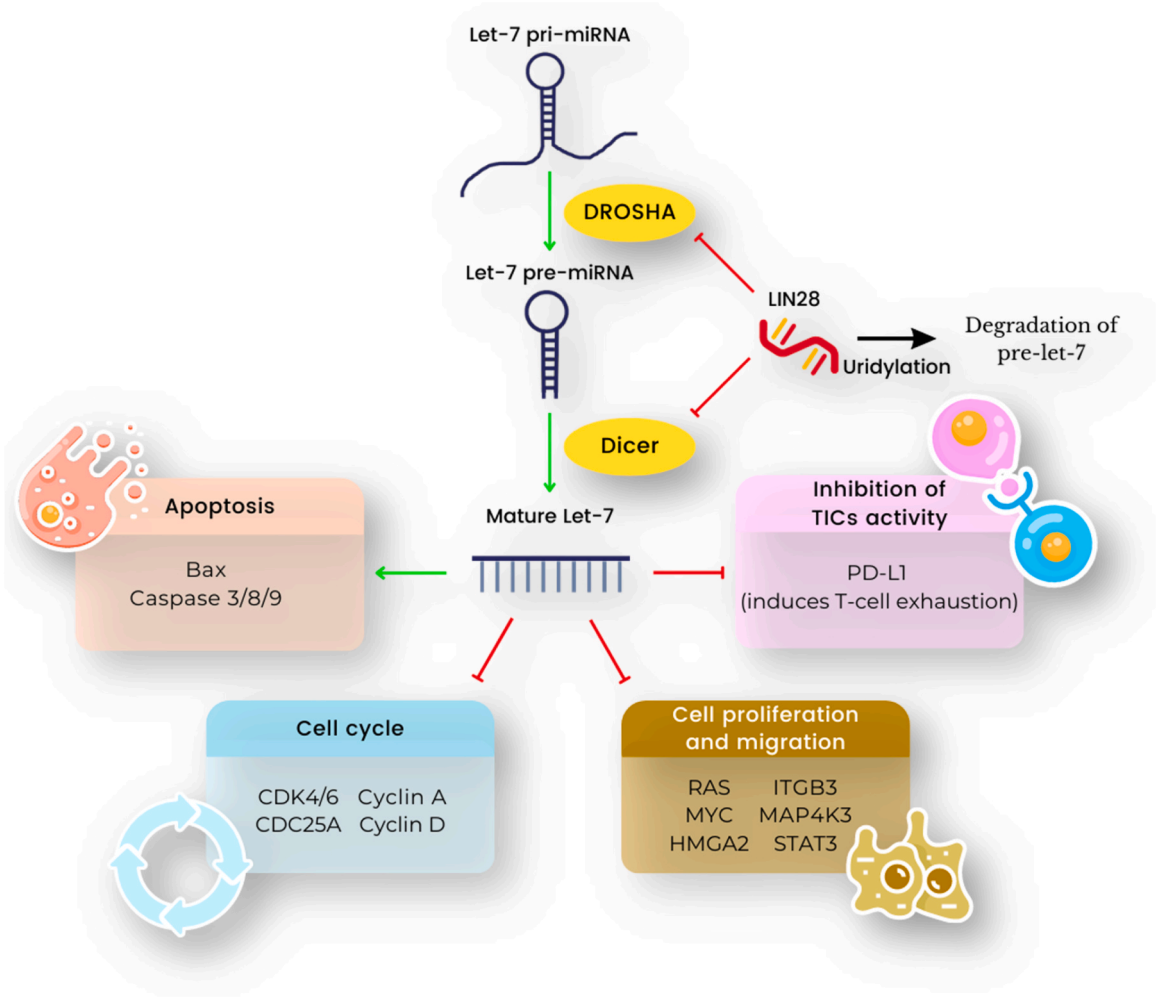

Fig. 7. Functions of let-7 tumour suppressor miRNA in lung cancer. Let-7 expression is regulated by LIN28A/B; LIN28 can repress the biogenesis of mature let-7 miRNA by binding to it and inhibit the miRNA processing enzymes. It also recruits TUTase to uridylate pre-let-7 which leads to its degradation. Mature let-7 exhibits tumour suppressive activity by downregulating cell cycle genes, oncogenes, and PD-L1 expression, while inducing apoptosis by upregulating the proapoptotic gene expression.

wild-type EGFR gene can also confer acquired resistance to third-generation EGFR TKIs, likely because of overexpression of the wild-type EGFRs due to mutant-selective inhibitory pressure of the third generation TKIs [156]. In 2021, a group of Japanese researchers reported that amplification of EGFR-mutant also led to acquired resistance to a third generation TKI (TAS-121). In the study, TAS-116 which is a heat shock protein 90 (HSP90) inhibitor has been shown to overcome the resistance, warranting further investigations into the potential therapeutic benefits of HSP90 inhibition in patients harbouring this type of TKI resistance [152].

2.4.2. *ALK*

Anaplastic lymphoma kinase (*ALK*) translocation occurs in 5–8% of NSCLC, and is particularly enriched in female, non-smokers, and younger patients [157]. The most common ALK fusion oncogene in NSCLC is echinoderm microtubule-associated protein-like 4 (EML4)–ALK, which occurs in 4–7% of NSCLC patients [158–160] and *ALK* genes are mapped to chromosome 2p21 and chromosome 2p23 respectively, in opposite orientations [158]. An inversion of chromosome 2, inv(2)(p21p23) generates the *EML4-ALK* fusion transcripts which encode a constitutively active chimeric tyrosine kinase with transforming activity [158,159].

Crizotinib, ceritinib and lorlatinib are TKIs used extensively to treat ALK-rearranged tumours. Crizotinib is the first-generation ALK inhibitor and has been shown to significantly improve ORR (65%) and PFS (7.7 months) compared to cytotoxic chemotherapeutic agents with ORR and PFS of 20% and 3.0 months, respectively [161], thereby establishing it as a standard treatment for advanced ALK-positive NSCLC. Superiority of crizotinib to standard platinum-based chemotherapy in advanced NSCLC patients with ALK rearrangement was also evident in the phase III PROFILE 1007 and PROFILE 1014 trials [161,162]. However, relapses have been observed within the first year of treatment in majority of the patients treated with crizotinib, attributed to the development of acquired resistance to ALK TKIs [163]. Hence, this gives rise to the development of second-generation TKIs ceritinib and alectinib [164].

Intrinsic or primary resistance to TKIs refers to patients who do not respond well with TKIs or only respond for a short period of time ($\leq$2 months) [165,166]. Conversely, acquired resistance refers to disease progression after a period of evident objective response with TKIs [167]. In 2010, Choi and colleagues first provided insight into the mechanisms of acquired crizotinib resistance by discovering two secondary mutations (L1196M and C1156Y) within the ALK tyrosine kinase domain [163]. L1196M mutation is the most common mutation in crizotinib-resistant NSCLC [168], which represents a point mutation of a residue in the ATP-binding pocket (gatekeeper position) leading to alterations in the conformational structure of kinase domain that interferes with TKI binding [163,169]. C1156Y is an activating mutation which occurs adjacent to the N-terminal of αC helix that is crucial for

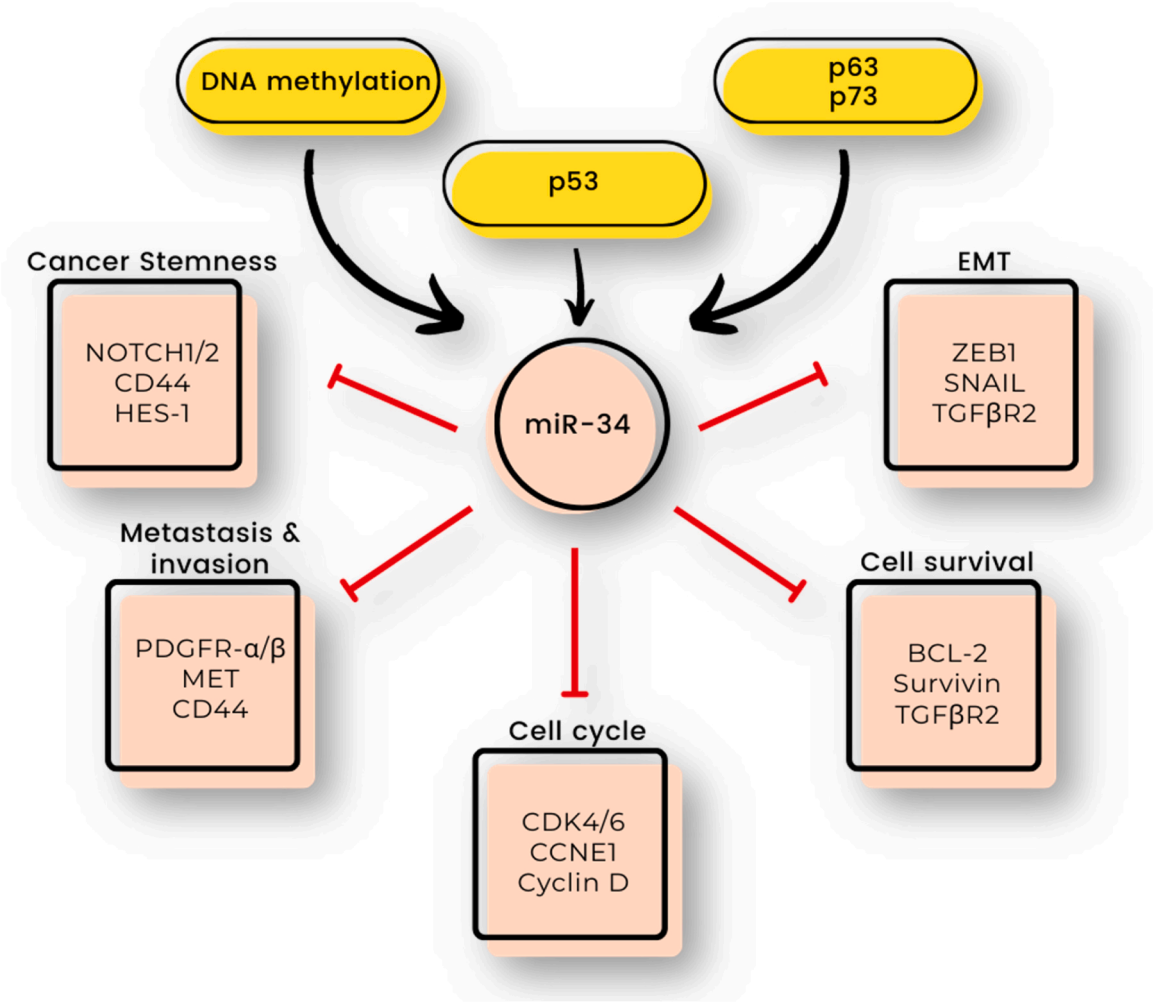

Fig. 8. The multifunctional roles of miR-34 family in suppressing tumourigenesis by binding to and regulating the target gene expression. p53 is the primary transcription activator of miR-34 which is activated in response to oncogenic stimuli and DNA damage. miR-34 family members exhibit tumour suppressing effects by inhibiting important cell signalling pathways such as the NOTCH, PDGF, MET, and TGF-β signalling which govern EMT and metastasis; by inducing cell cycle arrest and apoptosis; and by inhibiting cancer stem cells and cell proliferation. In LSCC, miR-34a inhibits CD44 which is a cell surface adhesion receptor highly expressed by cancer stem cells (CSCs) that promotes migration, invasion, and angiogenesis.

allosteric regulation, thus resulting in steric hindrance for the binding of TKIs to the ATP-binding site [163,170].

Since then, several secondary mutations throughout the ALK kinase domain have been identified. For instance, G1269A constitutes the second most prevalent mutation after L1196M in crizotinib-resistant patients; other individual mutations including C1156Y, G1202R, S1206Y, F1174C, and I1171T were also reported in smaller number of cases [168,171]. Interestingly, I1171X and G1202R substitution mutations were more commonly reported in alectinib-resistant cases compared to other types of ALK TKI-resistant cases, whereas G1202R mutation predominated in ceritinib- and beigatinib-resistant NSCLC [168]. Other than secondary mutations in the ALK tyrosine kinase domain, wild-type *EML4-ALK* fusion gene amplification was also identified as an alternative mechanism for acquired resistance to crizotinib in NSCLC patients [172]. A study demonstrated that *ALK* copy number gain may exist concurrently with secondary mutations resulting in acquired crizotinib resistance, but a high level of *ALK* amplification alone was also sufficient to confer resistance [172]. Additionally, upregulation of bypass signalling pathways such as EGFR, KIT proto-oncogene, receptor tyrosine kinase (KIT), and insulin-like growth factor 1 receptor (IGF1R) may also contribute to crizotinib resistance [173]. Aberrant activation of these ALK-independent prosurvival bypass tracks will therefore require the combination of ALK inhibitor and the corresponding RTK inhibitor to overcome this off-target resistance [172].

However, the rationale for using this type of combinatorial therapy remains to be evaluated to date [174]. Although there are studies that have demonstrated the clinical benefits of the aforementioned treatment to a certain extent [175,176], but there also exists evidence supporting the notion that the benefits might not outweigh its negative impacts. For example, a study has proven that the dual inhibition of EGFR and ALK (dacomitinib combined with crizotinib) not only demonstrated low therapeutic efficacy, but also conferred inherent clinical toxicity [177]. 43% of patients experienced grade 3 or 4 treatment-related adverse events, including gastrointestinal side effects (particularly diarrhoea), rashes, and fatigue [177]. Moreover, the study conducted by Yang and colleagues revealed that the efficacy of the combination treatment with EGFR- and ALK TKIs in EGFR/ALK co-mutant NSCLC was associated with and therefore may be dependent on the differential phosphorylation levels of EGFR and ALK [178].

2.4.3. *KRAS G12C*

The human rat sarcoma viral oncogene family (*RAS*) comprises of Harvey rat sarcoma viral oncogene (*HRAS*), Kristen RAS (*KRAS*) and neuroblastoma RAS (*NRAS*) genes located on chromosome 11, 12, and 1 respectively [179]. The *RAS* gene encodes a guanosine triphosphatase

(GTPase) that consists of a catalytic G domain containing six β-sheets and five interconnecting α-helices in which guanine nucleotide binding takes place; a C-terminal hypervariable region (HVR) with CAAX motif which mediates trafficking of the protein to membrane [180,181]. The Ras proteins function as a binary switch that switches between inactive guanosine diphosphate (GDP)-bound state that is readily activated by guanine nucleotide exchange-factor (GEF) for GDP/GTP exchange; and active guanosine triphosphate (GTP)-bound state that can bind to its effectors or revert to the inactive state via GTPase-activating protein (GAP)-mediated GTP hydrolysis [181]. Activated Ras, which is located downstream of EGFR, HER2, and fibroblast growth factor receptor (FGFR) signalling pathways, can then transduce the stimulatory signal to its downstream signalling pathways involved in the regulation of cell proliferation, differentiation, and apoptosis, such as the PI3K/AKT/m-TOR and RAF/MEK/ERK signalling pathways [179,182].

Among the three isoforms of Ras family, *KRAS* is the most commonly mutated oncogene in cancer, accounting for over 80% of the *RAS* gene mutations [182,183]. *KRAS* mutations occur in approximately 25–30% of NSCLCs and almost all of the mutations occur in codons 12 and 13 of exon 2 [182,184]. In contrast to *EGFR* mutations, *KRAS* alterations are more frequently reported in the Western than the Asian populations [182,185]. Prior studies have indicated that KRAS mutations occurred in over 30% of LUAD [186,187], predominantly the *KRAS G12C* mutation, followed by the G12D and G12V subtypes [188,189]. Additionally, *KRAS* mutations are also associated with smoking status, which is likely attributed to the frequent oncogene alterations caused by tobacco carcinogens [182,190]. On the other hand, *KRAS* mutations only occur in up to 16.2% of SCLC patients, with exon 3 mutations being the most frequent incidence [191], contrary to the frequent exon 2 mutation in NSCLC. Multiple lines of studies have reported that *KRAS* mutations frequently co-occurred with other gene mutations in NSCLC, such as the tumour suppressor genes *TP53*, *STK11*, *KEAP1* and *ATM*, as well as the driver oncogenes *MET*, *HER2*, *EGFR* and *BRAF* [192–194].

Sotorasib (AMG510) is an extensively evaluated KRAS G12C inhibitor (G12C-I) in clinical trials. It has been approved by US FDA in 2021 as a second-line treatment for advanced NSCLC with KRAS G12C mutation [195]. X-ray co-crystal structure analysis revealed that sotorasib binds irreversibly to the mutant cysteine residue near the P2 pocket of the mutant protein, trapping it in its inactive state and inhibiting GDP/GTP exchange [196,197]. It has also been shown to work synergistically with other targeted therapeutic drugs (e.g., erlotinib, trametinib and afatinib) and with immunotherapy in inhibiting tumour growth, highlighting its clinical value both in monotherapy or in combinatorial regimens for treating KRAS G12C-mutant tumours which are known for their intratumoural heterogenicity [197]. In the phase II CodeBreak 100 trial, a cohort of NSCLC patients harbouring KRAS G12C mutation treated with sotorasib resulted in ORR, disease control rate (DCR) and PFS of 37.4%, 80.5%, and 6.8 months, respectively [198,199]. These results have further validated the clinical efficacy and tolerability of sotorasib as demonstrated in phase I CodeBreak 100 trial, which reported that the ORR, DCR and PFS were 32.2%, 88.1%, and 6.3 months, respectively [200]. In the 2-year follow up, long-term treatment with sotorasib for more than 2 years in the cohort of patients reported clinical benefits with ORR, 2-year OS rate, and PFS of 41%, 33%, and 6.3 months [201]. The most common treatment-related adverse events were diarrhoea (30%), elevated alanine aminotransferase (18%) and aspartate aminotransferase levels (18%) and no reported fatal adverse events [201].

In the aforementioned clinical trials, it could be observed that the ORRs with G12C-I generally range between 30% and 40% with a median PFS of 6 months. The differential response observed in patients treated with G12C-I could be explained by an interesting study conducted by Xue *et. al*, where they identified a fitness mechanism adopted by the KRAS G12C cells which allowed them to escape inhibition [202]. They found out that some cancer cells in inactive (quiescent and drug-sensitive) state can synthesize new KRAS G12C cells in their active (drug-insensitive) states, which were perpetuated by EGFR and aurora kinase A (AURKA) signalling. On the other hand, intrinsic resistance is best demonstrated by an adaptive feedback mechanism where the inhibition of downstream ERK signalling could reactivate RTK-mediated signalling (signalling rebound) [203,204].

A clinical trial has characterized a group of adagrasib-resistant patients on the basis of resistance mechanisms into those who acquire secondary KRAS mutations or gene amplification; those who have co-occurring oncogenic alterations that activate alternative signalling pathways; and those who show LSCC transformation [205]. Since additional genetic alterations in the RTK/RAS/MAPK signalling pathway (*NRAS*, *BRAF*, *MAP2K1*, *BRAF*, and *FGFR3*) are frequent events in patients who developed resistance (37% of the resistant cases) [205], this has prompted the search for combination treatment regimens that could effectively suppress both KRAS G12C and the aberrated pathways. Evidently, a study showed that co-inhibition of intermediates of the downstream ERK signalling could enhance the antiproliferative effect of G12C-I in tumours that acquired secondary *RAS* or *BRAF* mutations [206]. On the other hand, upstream co-inhibition of Src homology region 2 domain-containing phosphatase-2 (SHP2) was also shown to enhance response to G12C-I in KRAS G12C-mutant NSCLC models, by blocking the RTK-dependent adaptive feedback mechanism and promoting proinflammatory TME [204].

All in all, these results supported the rationale for drug combinations in treating patients who progressed on or after treatment with G12C-I. However, the diverse genetic mutations and resistance pattern in KRAS G12C tumours may impede the search for an effective therapeutic strategy to conquer resistance mechanisms that emanate as patients receive G12C-I treatment [206].

2.5. Gene editing (CRISPR-Cas9)

Clustered regularly interspaced short palindromic repeat and CRISPR-associated proteins (CRISPR-Cas9) system has emerged as an attractive option for treating various types of cancers [207]. CRISPR-Cas9 is a simple, specific, and accurate genome editing tool widely used in cancer research in the identification of target genes (oncogene, tumour suppressor gene, and drug-resistance gene), construction of specific gene knockout animal models, gene therapy. In lung cancer treatment, CRISPR-Cas9 could target the proto-oncogenes and tumour-suppressor genes associated with tumourigenesis, evaluate genes related to chemotherapy drug and targeted drug resistance, as well as targeting the T-cells [208].

Scientists have proposed the use of CRISPR-Cas9 to target and correct the oncogenic mutated *EGFR* sequence in NSCLC by: (1) homology-directed repair (HDR), where the Cas9 is used to create single- or double-strand nicks and subsequent DNA repair on the mutated sequence to replace it with wild-type sequence; and (2) destructing the mutated *EGFR* DNA sequence via HDR-mediated stop codon insertion or non-homologous end joining (NHEJ)-mediated random insertion and deletion [209]. A study conducted using a mouse lung cancer xenograft model has shown that CRISPR/Cas9-mediated knockout of an oncogenic mutant *EGFR* allele has resulted in a significant reduction of tumour growth [210]. In this study, the researchers utilized CRISPR-Cas9 to specifically target and disrupt the *EGFR* allele harbouring the L858R missense mutation.

CRISPR-Cas9 gene-editing technology may also be utilized to repair the mutated tumour suppressor genes and reinstate their antitumoural functions. A study involving the use of CRISPR-Cas9 knockout of Kelch-like ECH-associated protein 1 (*KEAP1*) in a KRAS-driven mouse model of LUAD showed that there was an increase in tumour proliferation and tumour burden due to hyperactivation of nuclear factor erythroid 2–related factor 2 (*NRF2*) [211]. Another study showed that the tumour suppressor miR-1304 knockout developed by CRISPR-Cas9 significantly increased heme oxygenase-1 (*HMOX-1*) expression, which led to cancer cell growth and survival in NSCLC [212]. Genes associated with chemotherapeutic drug resistance are also targets for CRISPR-Cas9 to

improve sensitivity of tumour cells to chemotherapy and enhance drug efficacy in lung cancer. In a study, *ERCC1* knockout using CRISPR-Cas9 showed increased cisplatin sensitivity in lung tumour cells especially in cells that have retained wild-type p53 [213]. In another study, CRISPR-directed *NRF2* knockout in A549 cells noted a decrease in cancer cell proliferation; the cells were also more sensitive to cisplatin and carboplatin [214].

A ground-breaking clinical trial of CRISPR-Cas9 on human subjects was conducted by a group of Chinese scientists in 2016 [215]. In this trial, they used nucleofection to deliver Cas9 and sgRNA plasmids into T-cells to disrupt the *PD-1* genes, and the edited T-cells were then expanded and transferred back to the patients to improve T-cell anti-tumour cytotoxicity. Among the enrolled 12 patients, the PFS was 7.7 weeks and OS was 42.6 weeks, with low incidence of off-target events. Therefore, it was concluded that this CRISPR-based therapy is safe and feasible for clinical application in patients with advanced lung cancer.

CRISPR-Cas9 technology, while promising, has several limitations in cancer treatment. Firstly, off-target effects are still a major challenge of CRISPR-Cas9 systems, which is described as unintended genetic modifications in locations other than the intended target. Off-target effects may stem from several factors, including the imperfect matches between the sgRNA and target DNA, low sgRNA specificity, flexibility of Cas9 enzyme, and off-target delivery. To minimize off-target effects, it is imperative to design highly specific gRNAs using bioinformatics tools and consider employing Cas9 nickase (Cas9n), which is a Cas9 variant that can generate single-stranded breaks (SSBs) [216]. This approach employs a pair of sgRNAs to create individual nicks on opposite strands of the DNA at the desired location, resulting in the generation of a double-stranded break (DSB) and initiate the high-fidelity BER pathway at the intended sites [216]. A number of Cas9 variants have been engineered to reduce off-target effects, such as SpCas9-HF1, hypaCas9, evoCas9, SaCas9, and HiFiCas9 [217,218]. The specificity of gRNAs may also be improved by extending their length at the 5' end and via chemical modifications [217]. Efficient delivery of the CRISPR-Cas9 system is another major obstacle to its clinical application. An ideal delivery system should effectively and precisely deliver the CRISPR components to target tissues or organs with minimal off-target effects and elicit minimal Cas9-specific immune response. Researchers are exploring various delivery methods, including viral vectors (adeno-associated virus and lentivirus), nanoparticle delivery, and physical delivery (electroporation, microinjection) [218].

A concerning issue with the CRISPR-Cas9 technology is the fact that it triggers Cas9-specific immune response that limit the effectiveness of the gene-editing process [219]. The widely utilised Cas9 variants, SpCas9 and SaCas9, which are derived from *Streptococcus spp.*, might elicit immunological responses in naïve humans [218,219]. On the other hand, people with pre-existing immunity against the bacterial strain might already have existing antibodies that recognize Cas9 eliciting immune responses [219]. Moreover, the commonly employed method of delivery involves viral vectors which can trigger adaptive immune response or pre-existing immunity in recipients [219].

The widespread implementation of CRISPR technology faces substantial ethical issues due to germline genome editing, which involves editing the genome of human gametes, fertilised eggs, or embryos [220]. However, it is critical to distinguish between germline editing, which a more controversial topic due to the possibility of unforeseen genetic mutations that could be passed down through the generations [220], and therapeutic somatic cell editing, which involves editing the genome of non-heritable cells and is relevant in the context of lung cancer treatment. Genome editing in somatic cells is more morally justifiable acceptable, as long as the individuals underdoing CRISPR-Cas9 interventions have provided informed consent and are well aware of the uncertainties, unintended risks, and potential benefits of genome editing [220]. This is particularly relevant to forthcoming CRISPR-Cas9 clinical trials for lung cancer treatment, where it is imperative to make sure patients are fully informed about the experimental nature of the treatment, associated risks, and unexpected outcomes. Likewise, it is necessary to fully understand the long-term effects of CRISPR-Cas9 treatment in humans by conducting in-depth research to evaluate potential risks or benefits over an extended period of time. The risk-to-benefit ratio must be carefully considered in terms of on-target and off-target rates, and unknown long-term effects for it to be implemented in clinical settings. Furthermore, accessibility and equity remain a conscientious issue with CRISPR-Cas9 technology. Since this is an expensive technology, it can be difficult to guarantee that everyone in the society has equal access to its benefits, especially in the case of the impoverished population and developing countries. The scientific community, pharmaceutical companies, and governmental organisations should collaborate to address this issue by increasing research funding and developing more cost-effective technologies to make the CRISPR-Cas9 technology more accessible and affordable. Furthermore, international collaboration between researchers and governments could help guarantee that this cutting-edge technology is available globally, including in underdeveloped nations.

2.6. Targeted miRNA drug therapy

MiRNA drug therapy involves the development and application of drugs targeting specific miRNAs for therapeutic purposes. Currently, miRNA-based therapies are based on several strategies—anti-miRNA oligonucleotides (AMOs), small molecule inhibitors, and miRNA mimics to inhibit overexpressed or oncogenic miRNAs and to replace or supplement the function of downregulated or tumour-suppressive miRNAs, respectively [221]. In lung cancer model, intranasal administration of let-7 reduced tumour formation in vivo [222]. Similarly, systemic delivery of let-7 and miR-34a in mouse model of NSCLC also successfully reduced tumour burden [223], suggesting that miRNA-based therapeutic using miRNA mimics may represent a novel treatment avenue for lung cancer treatment. To date, researchers have unveiled several miRNAs, such as miR-34a, miR-126, miR-218–5p, miR-433, and miR-497, that target certain mRNA and the downstream signalling pathways that control cell proliferation (Cyclins E1 and E2, PTEN, ITGA6, VEGF-A, and HDGF), and confer resistance to radiotherapy (PRKDC), chemotherapy (TMED5), and targeted therapy (MNK and BMF) in preclinical studies [224].

There are a small number of miRNA-based therapeutics in clinical trials in human lung cancer, such as TargomiRs (NCT02369198), MRX34 (NCT01829971), and INT-1B3 (NCT04675996) [225]. TargomiRs contains a double-stranded miR-16-based microRNA mimic delivered by the bacterial minicells (nanoparticles)—EnGeneIC Dream Vectors (EDVs) to restore the tumour suppressive function in patients with recurrent malignant pleural mesothelioma and NSCLC [226]. Phase I clinical trials reported moderate response and was well tolerated and safe in the patients [226]. On the other hand, MRX34 is a liposomal miR-34a mimic that was the first trial conducted in humans and reached Phase I clinical trials for various cancers such as primary liver cancer, lymphoma, melanoma, multiple myeloma, renal cell carcinoma, SCLC, and NSCLC [227]. Although they noted a dose-dependent modulation of miR-34a target genes, the clinical trial was terminated owing to serious immune-mediated adverse events and resulted in four patient deaths [225]. Nevertheless, the study provides valuable insights into the complexities and challenges associated with developing miRNA-based drugs for oncology, and necessitates future development to address limitations for effective delivery of miRNA mimics and questions related to the role of downstream genes targeted by miR-34a and the unexpected immune-related toxicity in humans not observed in animal studies [227]. The drug INT-1B3 is a lipid nanoparticle (LNP)-formulated miR-193a-3p mimic (1B3) [228]. Preclinical studies on various human cancers such as triple-negative breast cancer (TNBC), NSCLC, melanoma, colon cancer, and hepatocellular carcinoma yielded promising results; treatment with INT-1B3 upregulated the tumour-suppressive PTEN pathway and supressed multiple key oncogenic signalling [229].

Hence, early phase clinical trials are currently underway to evaluate the safety, pharmacokinetics and pharmacodynamic profiles, and preliminary efficacy of the drug in patients with advanced solid tumours [228].

3. Tumour suppressor genes in lung cancer

Several data sources have stipulated that the emergence of cancers is a multi-step process whereby the normal cells will have to accumulate several genetic alterations (somatic and germ-line mutations), in order to transform into a malignant state [230,231]. According to Hanahan and Weinberg, during the multi-step process, the cancer cells acquire the six hallmark capabilities of: sustaining proliferative signalling, evading antiproliferative signals, resisting apoptosis, immortalization, sustaining angiogenesis, and tissue invasion or metastasis [230,232].

Based on The Cancer Genome Atlas (TCGA) which characterized over thousands of tumour cases across over 60 primary cancer sites, the top five most commonly mutated genes in human cancers are, in decreasing order: *TP53*, *MUC16* (*CA125*), *CSMD3*, *LRP1B*, and *PIK3CA* [233]. Among those, *MUC16* and *PIK3CA* are proto-oncogenes [234,235], whereas *TP53*, *CSMD3*, and *LRP1B* are tumour suppressor genes (TSGs) [236–238]. TSGs can be categorized into "gatekeeper" genes that regulate cell division, proliferation, and apoptosis; or "caretaker" genes that maintain the genomic integrity [239]. TSGs can also be categorized into five types based on the antitumour mechanisms of their encoding proteins: (1) Genes that encode protein involved in cell cycle regulation; (2) Genes that can inhibit cell proliferation by encoding a signal receptor or transducer protein; (3) Genes that encode checkpoint regulatory proteins which detect DNA damage and illicit cell cycle arrest; (4) Genes that encode pro-apoptotic proteins; and (5) Genes that encode proteins associated with DNA damage repair [240].

Most of the TSGs inactivation follow the Knudson's two-hit model hypothesis, which assumes that TSGs are recessive in cellular level and that both alleles must acquire loss of function mutations in order to result in carcinogenesis [241,242]. In sporadic cancer, the first hit event of this paradigm involves genetic (point or deletion mutations) or epigenetic (hypermethylation) inactivation of one allele, followed by a second mutation (chromosomal deletion) in the remaining functional allele in a single somatic cell [243,244]. Meanwhile, individuals with hereditary cancer would have acquired the first hit (susceptibility gene) at birth due to a germline mutation, followed by LOH of the normal allele owing to somatic mutation [243,244]. Some of the tumour suppressor genes that follow this two-hit paradigm are *TP53*, *RB1*, *BRCA1*, *MSH2*, and *PTEN* [240].

Cancer development is triggered by the accumulation of genetic and epigenetic alterations [245]. Genetic changes are consequences of aging, exposure to mutagens, and UV irradiation that result in large scale alterations of chromosomal structure (translocations and inversions) or smaller scale mutations affecting the nucleotide sequences (frameshift and point mutations) [246,247]. On the other hand, epigenetic alterations are induced primarily due to aging, chronic inflammation, and infections [245]. Epigenetic machineries include post-transcriptional regulation (miRNA interference), DNA methylation (promoter hyper- or hypomethylation), nucleosome remodelling (nucleosome sliding or assembly, and histone exchange), and histone modifications (acetylation, methylation, and ubiquitination) [248,249].

Loss of heterozygosity (LOH) refers to the loss of one of the two parental alleles, with the remaining allele being subjected to inactivating mutation (hypermethylation or point mutation) [244]. This allelic imbalance is created by copy number alterations (CNAs) through copy number loss LOH (CNL-LOH) which emerged from full or partial chromosomal deletion, resulting in the loss of a wild-type allele of a gene; or through copy number neutral LOH (CNN-LOH) where uniparental disomy (UPD) or gene conversion occurred with concurrent allelic loss, resulting in the presence of two mutant alleles without a net change in gene copy number [250].

LOH on chromosomes 3p, 5q, 9p, 13q, and 17p are common in both SCLC and NSCLC [251]. Studies using the comparative genomic hybridization (CGH) approach to screen genomic alterations in SCLC tumours revealed that allelic deletions on chromosomes 3p, 4q, 5q, l0q, 13q and 17p were characteristic of SCLCs [252,253]. A genome-wide allelotyping using high resolution microsatellite markers revealed several loci with prominent (>60%) allelic loss on the chromosomes 1q, 3p, 4, 5, 9q, 10, 13q, and 17p in SCLC; and on chromosomes 1p, 8p, 9p, 13q, 17p, 19p, as well as chromosome X in NSCLC. In addition, this study also identified distinct allelic loss hotspots between SCLC and NSCLC, in which NSCLC had more (n = 22) regions of frequent LOH than SCLC (n = 17), indicating the possible number of tumour suppressor genes inactivated in lung cancer [254]. In LUAD, the incidence of LOH is less frequent (21.4%) compared to LSCC (64.3%) in the four loci: 3p21 (*MLH1*), 5q11–13 (*MSH3*), 9p21 ($p16^{INK4a}$) and 17p13 (*TP53*). Besides, they also found out an association between LOH at 3p14 (*FHIT*) and the aforementioned loci with smoking status, suggesting that the loss of these genes may be responsible for the differential sensitivity to tobacco carcinogen exposure, that is, the DNA adduct burden [254]. These findings were consistent with another study, in which LOH was found to be associated with smokers with LUAD having a significantly lower rate (67%) than LSCC (90%) [255].

COSMIC (Catalogue Of Somatic Mutations in Cancer) is the world's most comprehensive resource for exploring somatic mutations in human cancer [119]. The COSMIC database is a collection of curated data generated by the Pan-Cancer Analysis of Whole Genomes (PCAWG) dataset, an extensive amount of published papers, and The Cancer Genome Atlas (TCGA). By referring to the GRCh38 COSMIC v96, among the top 20 most frequently mutated genes in SCLC, *TP53*, *RB1*, *LRP1B*, *KMT2D*, *FAT4*, *FAT1*, *NOTCH1*, *CREBBP*, *EP300*, *GRIN2A*, *ZNF521*, *ARID1A*, and *PTEN* are tumour suppressor genes. In NSCLC, the most frequently mutated TSGs are *TP53*, *ARID1A*, *KMT2D*, *KEAP1*, *FAT1*, *ATM*, *SMARCA4*, *NF1*, *STK11*, *TET2*, and *CDKN2A*. Table 1

3.1. Chromosome 1p

3.1.1. ARID1A

AT-rich interactive domain-containing protein 1A (ARID1A) is mapped onto chromosome 1p36.11 and encodes brahma-related associated factor 250a (BAF 250a), which is a component of the switch/sucrose nonfermenting (SWI/SNF) complex [256]. SWI/SNF is a chromatin-remodeling complex that utilizes ATP to alter the chromatin structure by first binding to the nucleosomal DNA and breaking the DNA-histone contacts, followed by the formation of intranucleosomal DNA loops which provides accessible binding sites for transcription factors [257,258]. ARID1A protein consists of an AT-rich interacting domain (ARID) with DNA-binding activity, and a C-terminal domain consisting of multiple LXXLL sequence motifs for protein-protein interaction [259]. ARID1A is essential for mammalian embryonic development, regulating differentiation of pluripotent stem cells, maintenance of stem cell pluripotency and genomic integrity [256,259].

ARID1A gene mostly functions as a tumour suppressor in a wide array of cancers, as it was often downregulated by loss of function (LOF) mutations [259]. Paradoxically, it has also been shown to promote tumour formation in a few *in vivo* cancer models, indicating that its tumour suppressive and oncogenic functions may be influenced by the tumour's genotypic profile and phases of tumour progression [259]. ARID1A is also implicated in lung cancer; it was downregulated in both NSCLC tumour samples and cell lines, which was associated with enhanced cell proliferation, resistance to chemotherapy and nodal stages [260]. In the study, ARID1A has been shown to play a role in controlling lung cancer cell proliferation by interacting with AKT and cyclin D1 proteins, and the antiapoptotic gene *BCL-2*. A genomic profile of constructed using the cell-free DNA (cfDNA) assay revealed that *ARID1A* mutations were present in 12% of LUAD patients and had concurrent mutations of *TP53*, *KRAS*, and *EGFR* in 79%, 35%, and 22%

Table 1
The table summarizes important information about tumour suppressor genes that are either frequently mutated and/or located on the chromosomal arms having high LOH rates in lung cancer.

Gene	Chromosome Location	Functions/Pathways	Expressions/Genetic Alterations in Lung Cancer	Clinical Implications
ARID1A	1p36.11	Component of the SWI/SNF complex, regulates chromatin structure	Downregulated in NSCLC predominantly by LOF mutations, co-mutations with TP53, KRAS, and EGFR	Enhanced cell proliferation, chemotherapy resistance, EGFR TKI resistance, shortened PFS, increased TMB, enhanced clinical efficacy of ICIs
FOXD3	1p31.3	Transcription regulator, crucial for maintaining pluripotency, repression of TIC promoter (WDR5)	Downregulated in lung cancer and TICs	Increased tumourigenesis, EMT, metastasis, and chemotherapy sensitivity, enhanced oncosphere formation
LRP1B	2q22.1-q22.2	LDLR superfamily member, involved in endocytosis	Mutations associated with higher TMB in NSCLC	Higher TMB, enhanced immune response in NSCLC, paradoxically better survival outcomes with immunotherapy
FHIT	3p14.2	A member of the histidine triad gene family on FRA3B, involved in mitosis, cell cycle control, frequently inactivated in cancer	Frequently hypermethylated in NSCLC, more prevalent in Asians, associated with squamous cell carcinoma subtype	Poor prognosis, association with HPV-mediated lung tumourigenesis, involvement in cisplatin resistance in NSCLC, diagnostic value in Asian NSCLC patients,
RASSF1A	3p21.31	Regulates microtubule and genomic stability	Downregulated in NSCLC by promoter methylation, may occur concurrently with other genes on the same locus, leads to decreased expression of downstream genes TAGLN and SPARC	Poor prognosis, increased tumourigenesis, EMT, invasiveness
FAT1	4q35.2	Cadherin superfamily member, involved in cell mobility, exhibits both tumor-suppressive and oncogenic effects, suppresses tumor-initiating ability of NSCLC cells	Downregulated in NSCLC, mutations associated with high TMB	Increased tumourigenesis, stemness, EMT, and metastasis, potential immunotherapy predictor, may regulate TME and immune response
FAT4	4q28.1	Cadherin superfamily member, crucial for planar cell polarity, preferentially tumor-suppressive	Downregulated in NSCLC	Low expression is a negative prognostic factor, especially in LUAD, overexpression inhibits metastasis in a MAPK-dependent manner
CDKN2A	9p21.3	Encodes p16INK4a and p14ARF, regulates cell cycle	Promoter hypermethylation of p16 correlates with poor prognosis, promoter hypermethylation of p14ARF is more frequent in LUAD than LSCC.	Associated with increased risk of cancer, potential prognostic marker, mutual exclusivity between p14ARF and p53 aberrations in LUAD
PTEN	10q23.31	Encodes PIP_3 that antagonizes PI3K/AKT/mTOR signaling pathway.	Downregulated in NSCLC by LOF mutations and hypermethylation, associated with squamous cell carcinoma subtype, concurrent allelic loss in EGFR-mutated NSCLCs	Poor prognosis, increased tumourigenesis, cancer cell proliferation and invasion
RB	13q14	Downstream effector of the p53 pathway, regulates cell cyle and apoptosis	Frequent allelic loss in SCLC but rare in NSCLC	Increased tumourigenesis and metastasis, potential therapeutic target for reactivation
Klotho	13q12.1	Anti-ageing gene	Downregulation associated with tumourigenesis	Potential tumor suppressive role in lung cancer, interaction with Rab 8 GTPase may enhance its tumor suppressing effec
TP53	17p13.1	Regulates cell cycle and apoptosis	Frequent mutations in SCLC and NSCLC	Poor prognosis, resistance to chemotherapy and radiation, potential therapeutic target for reactivation
KEAP1	19p13.2	Encodes Keap1 protein involved in the oxidative pathway	Somatic mutations in LUAD, LOH predominantly occurs with missense mutations, frequent co-mutations with STK11 and KRAS	STK11/KEAP1 co-mutation associated with poor prognosis, compromised immunotherapy efficacy, resistance to ferroptosis cell death, and upregulation of SCD1 (potential therapeutic target). KRAS/KEAP1 co-mutation associated with poor prognosis, reistance to chemotherapy and immunotherapy, and increased dependency on glutaminolysis (glutaminase as potential therapeutic target)
STK11	19p13.3	Encodes LKB1 involved in the AMPK pathway which regulates cellular metabolism	Frequent mutations in NSCLC, especially LUAD, frequent co-mutation with KRAS	STK11/KRAS co-mutation associated with compromised immunotherapy efficacy, increased sensitivity to HSP90, and dependence on DTYMK, CPS1, and GFPT2 (potential therapeutic targets)

of *ARID1A* mutated cases, respectively [261]. In a cohort of 2440 NSCLC patients, ARID1A alterations were observed in 7.5% of the tumour samples and were predominated by LOF mutations (69%), which were responsible for the complete loss of ARID1A protein expression. Additionally, this study also demonstrated that ARID1A mutations were more likely to have concomitant TP53 mutations (69%), rather than EGFR driver mutations (9%) [262].

A recent study depicted that *ARID1A* mutations may be predictive for response to EGFR TKI and were associated with shorter PFS in advanced NSCLC patients [263]. Evidently, *ARID1A* loss has been shown to play a part in governing EGFR TKI resistance in NSCLC patients due to aberrant activation of the signalling pathways involved in the resistance mechanisms, including PI3K/AKT, NFκB, and JAK/STAT pathways [264]. Interestingly, *ARID1A*, *ARID1B*, and *ARID2* gene mutations were shown to increase tumour mutation burden (TMB) and neoantigen load, which resulted in enhanced clinical efficacy in NSCLC patients treated with ICIs [265]. In fact, *ARID1A* loss may have been associated with ICI efficacy by increasing PD-L1 expression and mutation load, as well as by inducing a proinflammatory TME [266].

3.1.2. *FoxD3*

Forkhead box D3 (*FOXD3*) gene located on 1p31.3 belongs to the forkhead box (Fox) transcription factor family which encodes forkhead protein with multifaceted roles as a transcriptional regulator [267]. It is crucial for maintaining pluripotency of murine ESCs (mESCs) while inhibiting their differentiation into endodermal, mesodermal or trophectodermal lineages [268]. In human ESCs (hESCs), FoxD3 overexpression led to EMT and paraxial mesoderm differentiation which

gives rise to chondroblasts and myoblasts during somitic development [269]. Conversely, loss of function of FoxD3 resulted in concurrent endodermal and mesodermal differentiation in addition to cell death, suggesting that FoxD3 expression is needed to suppress hESCs differentiation and maintain self-renewal and survival [269]. FoxD3 is downregulated in several cancers including colorectal cancer [270], hepatocellular carcinoma [270], and breast cancer [271].

The tumour suppressive function of FoxD3 in lung cancer was first demonstrated in a study where it was significantly downregulated by 20-fold compared to normal lung tissue, which increased the expressions of IGF1R and the oncogene B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) that drive tumourigenesis [272,273]; whereas the negative cell cycle regulator p21 expression was suppressed [274]. In a recent study, FoxD3 was downregulated in lung cancer tumour initiating cells (TICs), which are highly malignant and tumourigenic cells with tumour-initiating and self-renewal abilities [275]. FoxD3 depletion in lung cancer TICs increased the oncosphere (3D spherical formation of cancer stem cell culture) formation, colony expansion, osteoclastogenesis (indicative of bone metastasis), and increased sensitivity to the chemotherapy drug doxorubicin [276]. In addition, it was revealed that FoxD3 can directly repress the TIC promoter WDR5, suggesting that FoxD3 also regulates tumour metastasis and progression by controlling TICs expansion [276].

3.2. Chromosome 2q

3.2.1. LRP1B

The low density-lipoprotein receptor (LDLR) superfamily consists of seven closely related lipoprotein receptors: low-density lipoprotein receptor related protein 1 (LRP1), low-density lipoprotein receptor related protein 1B (LRP1B), megalin/LRP2, low-density lipoprotein receptor (LDLR), very low-density lipoprotein receptor (VLDLR), multiple epidermal growth factor-like domains 7 (MEGF7)/LRP4, and LRP8/apolipoprotein E receptor 2 (apoER2) [277]. LRP1 is a multifunctional receptor which plays diverse roles in maintaining cholesterol homeostasis and regulating cellular signalling pathways, which are essential for cell development and migration [277]. It mediates endocytosis by binding with multiple ligands such as lipoproteins, proteases, growth factors and cytokines [278]. Besides, it also has fundamental roles in signalling pathways in various tissues including blood vessels to control vascular smooth muscle cell proliferation and prevention of atherosclerosis [279,280]; in neurons to control blood-brain barrier permeability and neuronal response [281,282]; in lung to regulate inflammatory response by initiating phagocytosis upon binding to collectins [283]. *LRP1B* gene is frequently silenced in cancers by genetic alterations such as deletion mutations, point mutations, and frameshift mutations; and epigenetic mechanisms by CpG islands hypermethylation, histone modifications, and miRNA silencing [284].

Curated genomic data from 332 melanoma and 113 NSCLC samples of patients treated with immunotherapy revealed that *LRP1B* mutation was present in 31% of NSCLC patients, and was associated with higher TMB [285]. Paradoxically, patients with *LRP1B* mutation had better survival outcomes with immunotherapy [285], which also paralleled the findings in a retrospective review across multiple types of LRP1B-mutated cancer [286]. Although the mechanism behind the immunomodulatory functions of *LRP1B* inactivation was poorly understood, it was believed that its role in modulating clearance of extracellular ligands through endocytosis may regulate TME and mediate drug uptake [287,288]. In addition, antigen processing and presentation pathways were also shown to be upregulated in LRP1B-mutated tumours with increased tumour-infiltrating cells (CD8+ T-cell, CD4 memory T-cell and NK cells), which may have promoted immune response [285]. In a study, it was revealed that *LRP1B* mutation frequency is positively correlated with tumour grade in LUAD patients, suggesting that it may also contribute to tumour transformation and progression [289].

3.3. Chromosome 3p

3.3.1. FHIT (FRA3B)

Fragile histidine triad diadenosine triphosphatase (*FHIT*) gene is one of the histidine triad gene family members encompassing the common fragile site, FRA3B (3p14.2) [290]. Common fragile sites are regions on a chromosome prone to DNA damage (e.g., breaks and gaps) upon replication stress, thus serve as vulnerable sites for genetic alterations during carcinogenesis [291]. As a member of the HIT nucleotide-binding protein superfamily, it encodes the diadenosine polyphosphase (Ap_nA) hydrolase which catalyzes the hydrolysis of nucleotidic compounds such as diadenosine triphosphate (Ap3A) to adenosine diphosphate (ADP) and adenosine monophosphate (AMP) [292]. However, it also has multiple roles in regulating mitosis, cell cycle control, and cell death, all of which are associated with cancer development when deregulated [292]. Inactivation of *FHIT* gene due to hypermethylation of the CpG islands in promoter regions is frequently reported in multiple types of tumours, including NSCLC [293], laryngeal squamous cell carcinoma [292], and breast cancer [294]. Previously, a few systematic reviews and meta-analyses have found out that the rate of FHIT hypermethylation was higher in NSCLC compared to normal lung tissue [295,296], and this difference was more prominent in Asians than Caucasians [295]. This ethnic heterogenicity was also described in another study, suggesting that *FHIT* methylation status may provide diagnostic value in Asian NSCLC patients but not in Caucasian patients [297]. Other than that, *FHIT* hypermethylation was also associated with male gender, smoking status, poor prognosis, and the lung cancer subtype squamous cell carcinoma [295,296].

The association of FHIT hypermethylation and inactivation with LSCC subtype was evident in a study; the loss of FHIT protein expression was more prevalent in LSCC (96.3%) compared to LUAD (45.5%), which was attributed to predominantly LOH of FHIT gene (67.8%) [293]. The high incidences of *FHIT* LOH in smokers implies that tobacco carcinogens are the central driver of homozygous deletions, promoter hypermethylation, and aberrant transcripts of the *FHIT* gene locus in the FRA3B region [290,298]. *FHIT* gene was involved in the regulation of LIN28/Let-7 pathway and miR-17/92 clusters, both of which are known to play a role in tumourigenesis [299]. A compelling study conducted by a group of Chinese researchers revealed that *FHIT* loss may participate in HPV-mediated lung tumourigenesis, as it was significantly more frequent in HPV16/18-positive patients than non-infected patients [300]. They hypothesized that HPV-DNA may integrate at the FRA3B fragile site where *FHIT* gene is situated, silencing the gene while upregulating the E6/E7 oncogene, which in turn overrides the tumour suppressive action of p53 through degradation or mutation. Furthermore, *FHIT* LOH was also shown to partake in the development of cisplatin resistance in NSCLC patients, possibly through p53 upregulated modulator of apoptosis (PUMA) suppression mediated by the AKT/NFκB/-SLUG pathway [301].

3.3.2. RASSF

Ras association domain family (RASSF) comprises of two subclasses: C-terminal RASSF (C-RASSF) and N-terminal RASSF (N-RASSF), both containing a total of ten homologues. RASSF1 to RASSF6 are C-RAFF proteins containing one Ras association (RA) domain in the C-terminus, whereas RASSF7 to RASSF10 are N-RASSF proteins containing a RA domain in the N-terminus [302].

Ras-Association Family 1A (*RASSF1A*) is a well-known tumour suppressor gene located on the chromosomal locus 3p21.31 [303], where its downregulation is associated with tumour progression and poor prognosis in various cancers, such as lung [304,305], breast [306], gastrointestinal [307], and bladder cancers [308]. RASSF1A confers microtubule and genomic stability, which are crucial for controlled cell growth and motility [309,310]. A previous study has shown that RASSF1A could detain regulator of chromosome condensation 1 (RCC1) in the cytoplasm by inducing mammalian sterile 20-like kinase 2

(MST2)-mediated phosphorylation of RCC1 [311]. RCC1 can then interact with ras-related nuclear protein (RAN) GTPase and chromosome to ultimately establish the RAN-GTP concentration gradient that is essential for spindle assembly during mitosis [312]. In addition, the C-terminal SARAH domain of RASSF1A protein can also bind to and activate mammalian sterile twenty (MST) kinases, which then leads to the activation of the pro-apoptotic Hippo pathway [313,314]. It can also activate death receptor dependent cell death by associating with tumour necrosis factor receptor 1 (TNF-R1) or TNF-related apoptosis-inducing ligand receptor 1 (TRAIL-R1), and modulator of apoptosis (MOAP-1), forming the RASSF1A/TNF-R1/MOAP-1 or RASSF1A/TNF-R1/MOAP-1 complex [315,316].

RASSF1A is frequently silenced in NSCLC owing to methylation on its promoter region, which may occur concurrently with other genes on the 3p21.3, such as zinc finger MYND-type containing 10 (*BLU*) and semaphoring 3B (*SEMA3B*) [317,318]. Downregulation of RASSF1A leads to decreased expression of downstream genes transgelin (*TAGLN*; also known as *SM22*) and secreted protein acid and rich in cysteine (*SPARC*), which have been shown to play a part in the carcinogenesis of NSCLC [319,320]. A study has shown that haploinsufficiency of *RASSF1A* was sufficient to enhance lung tumourigenesis in KRAS-driven lung cancer mouse model by relieving RAS inhibition on Yes-associated protein (YAP) thereby blocking the Hippo pathway and upregulating IL-6 [321]. Interestingly, the main downstream signalling pathways of RAS (PI3K, RAF/MAPK, and RAL) were also activated in normal lung tissues to a similar degree as in KRAS-mutant tumours, indicating that increased activation of each of these pathways alone may be insufficient to result in tumourigenesis, which also applies to RASSF1A suppression [321]. RASSF1A loss may also contribute to EMT and invasiveness of lung cancer as a result of increased cofilin activation through rho/rac guanine nucleotide exchange factor 1/ras homolog family member B (GEFH1/RhoB) inhibition, and enhanced YAP transcriptional activation of EMT-associated genes [322].

3.4. Chromosome 4q

3.4.1. FAT1 & FAT4

FAT1 atypical cadherin 1 (*FAT1*) gene is an ortholog of the Drosophila Fat-like (Fat-like) gene and is located on 4q35.2 [323]. It encodes a member of the cadherin superfamily which is a group of large transmembrane proteins characterized by extracellular cadherin-type repeats, five epidermal growth factor (EGF)-like domains and one laminin G-like domain [323]. FAT1 protein can interact with Enabled/vasodilator-stimulated phosphoprotein (Ena/VASP) and Scribble proteins at the lamellipodia and filopodia (cytoskeletal and cytoplasmic extensions on the leading edge of migrating cells) to promote actin polymerization and cell mobility [323]. FAT1 is also involved in the regulation of several signalling pathways implicated in a broad array of cancers, for instance MAPK/ERK, Wnt, and Hippo pathways [324]. It exhibits both tumour suppressive and oncogenic effects in a tumour-specific manner [323]. For example, FAT1 may act as a tumour suppressor in oral and breast cancers by inhibiting cell proliferation [323]; conversely, a truncated version of FAT1 protein was markedly expressed in leukaemia and was shown to act in concert with NOTCH1 in tumourigenesis [325]. In NSCLC, FAT1 was found to be downregulated and its overexpression was a positive predictor of OS and PFS [326]. Notably, FAT1 could also suppress the tumour-initiating ability of NSCLC cells by supressing prominin-1 (PROM1/CD133), SRY-box transcription factor 2 (SOX2), and octamer-binding transcription factor 4 (OCT4) and the transcriptional activity of YAP1 by sequestering it in the cytoplasm [326]. Consistently, in a study using *FAT1* knockout mice of lung cancer, *FAT1* deletion was shown to promote tumour initiation, stemness, hybrid EMT state, and metastasis via upregulation of YAP1 and SOX2 [327].

Previously, a study was conducted to investigate the relationship between FAT family gene (*FAT1/2/3/4*) mutations with the prognosis and response to immunotherapy using online published data sets from TCGA and three clinical cohorts. Based on the whole-exome sequencing data, FAT family gene mutations occurred at high frequency (57.3%) in a cohort of NSCLC patients, which were significantly associated with high TMB and higher tumour infiltrating cells proportion in the TME of LUAD, all of which are important determinants of ICI efficacy [328]. Particularly, *FAT 4* mutations were shown to improve ORR in patients treated with ICIs, while *FAT2* mutations stood out as an independent good prognosis factor in LUAD patients. Together, these results provided the rationale for using FAT family gene mutations as predictors of prognosis and immunotherapy efficacy in lung cancer [328]. This was further supported by another recent retrospective analysis which found out that ICI-treated NSCLC patients harbouring *FAT1* mutations were enriched with proinflammatory activated CD4+ T-cells, effector memory CD4+ T-cells and M1 macrophage; and had lower proportions of immune suppressive T-regulatory cells and M2 macrophage, thus predicted favourable outcome with immunotherapy [329]. The tumour immunomodulatory roles of FAT family genes might be related to its regulation on YAP1 expression. Ample of studies have shown that YAP1 can create an immunosuppressive TME by upregulating PD-L1 and immune suppressive cytokines (CXCL5 and TNF-α), as well as recruiting immunosuppressive cells (MDSCs, T-regulatory cells, and M2 macrophages) which result in tumour progression and drug resistance [330,331]. Therefore, the combination of ICI with YAP1 inhibitor may exert synergistic effects in suppressing the growth of PD-L1 positive tumours [331].

FAT atypical cadherin 4 (*FAT4*) located on 4q28.1 is the ortholog of Drosophila Fat gene [323]. FAT4 is crucial for planar cell polarity (PCP) in epithelial tissue by interacting with multiple PDZ domain protein (MPDZ) to recruit membrane-associated guanylate kinase (MAGUK) p55 subfamily member 5 (MPP5). Unlike its homolog *FAT1*, *FAT4* is preferentially tumour suppressive [323]. In a recent study, FAT4 expression was shown to be lowly expressed in NSCLC tissues and was a strong negative prognostic factor, particularly in LUAD but not LSCC patients. On the contrary, FAT4 overexpression inhibited metastasis in a MAPK-dependent manner [332].

3.5. Chromosome 9p

3.5.1. CDKN2A

The $p16^{INK4a}$ gene is a prototype of the INK4 family, with the other three members being $p15^{INK4b}$, $p18^{INK4c}$ and $p19^{INK4d}$, all of which function as CDK inhibitors [333]. $p16^{INK4a}$, also known as cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and major tumour suppressor 1 (*MTS1*) maps onto the chromosomal locus 9p21.3. Its protein product, p16 has five ankyrin motifs with helix-turn-helix conformation which interact with kinase catalytic cleft and distort the ATP binding site, hence lead to inhibition of both the CDK and CDK4/6-cyclin D complexes [334]. Inhibition of CDK4/6 phosphorylation prevents the G1/S transition by keeping retinoblastoma protein (pRb) in its hypophosphorylated state [335]. *p16γ* and *p12* genes are splicing variants of p16 with tumour suppressive functions. p16γ is present in high levels in primary T- and B-cell acute lymphoblastic leukaemia (ALL) and has similar CDK4/6 inhibitory functions as p16 [336]. On the other hand, p12 exists primarily in pancreas and albeit having a similar structure as p16, it does not have regulatory effect on CDK4 and induces pRb-independent cell cycle arrest [337,338].

$p14^{ARF}$ is one of the upstream regulators of p53 (the other being MDM2) which induces cell cycle arrest and apoptosis in response to oncogenic stimuli and DNA damage [338,339]. $p14^{ARF}$ gene is generated through alternative splicing of exon 1β of $p16^{INK4a}$ onto exon 2 and exon 3. Since the alternative exon 1β was transcribed with a different promoter from exon 1α and allowed translation of exon 2 and exon 3 with a different alternative reading frame, hence this transcript variant encodes a different protein with distinct function from p16 [340]. p14ARF expression is induced by the proliferative signals of oncogenes including

adenovirus early region 1A (*E1A*), *RAS*, MYC proto-oncogene, bHLH transcription factor (*MYC*), and E2F transcription factor 1 (*E2F1*) [341–344]. On the other hand, oncoproteins such as POK Erythroid Myeloid Ontogenic factor (Pokemon), Twist, and Geminin are p14ARF transcription suppressors, whereby their overexpression could lead to tumourigenesis by inhibiting the ARF-Mdm2-p53 pathway [345–347]. Importantly, p14ARF can also retain Mdm2 in the nucleoli, thereby protecting the antiproliferative p53 from proteasomal degradation and enabling its transcriptional activity [348,349]. Previous studies have shown that p14ARF can also inhibit cell proliferation in p53-null or both p53- and Mdm2-null cells, suggesting that it can also induce p53-independent cell cycle arrest [350,351].

Sugimoto *et. al* showed that p14ARF (p19ARF in mouse) protein can retard cell growth by inhibiting rRNA processing in two ways: it can bind to 5.8S rRNA and interfere with the processing of 32S precursors [352]; it also interacts with nucleophosmin 1 (NPM1) and other nucleolar proteins essential for preribosomal maturation and nuclear export [353,354]. In addition, p14ARF also exhibits p53-independent tumour suppressive function by inhibiting E2F1 [355], c-Myc [356,357], NFκB [358], and hypoxia-inducible factor 1-alpha (HIF1α) transcription factors [359]. Previously, it has been reported that p14ARF was able to trigger p53-independent G2 cell cycle arrest in NSCLCs and NE lung tumours by cooperating with Tip60 to activate the ATM/CHK2 signalling pathway in response to DNA damage [360]. Reef and colleagues reported an interesting discovery on a novel translation product of $p14^{ARF}$, which they named it as short mitochondrial ARF (smARF). This isoform of p14ARF protein was localized in mitochondria and has high turnover rate; it differed from the full-length p14ARF in that it has no nucleolar functions (interaction with Mdm2) but was able to induce p53-independent cell death via autophagy [361].

A systematic review and meta-analysis found that p16 promoter hypermethylation was correlated with poor OS and shorter DFS in NSCLC [362]. Gutiontov *et. al* demonstrated that *CDKN2A* LOF in NSCLC patients treated with ICIs was associated with doubled disease progression rate and shorter PFS and OS [363]. Multiple lines of evidence showed that promoter hypermethylation of $p14^{ARF}$ is the primary mechanism in silencing of this gene and is more frequent in LUAD than LSCC [364]. A meta-analysis involving 11 Chinese patients with NSCLCs indicated that there were significant associations between $p14^{ARF}$ expression and NSCLC risk (OR = 11.02) and TNM stages (OR = 2.07) but not lymph node involvement (OR = 0.93) and differentiation status of tumours (OR = 0.57) [365]. Studies have found that there were inverse correlations between the expression status of p14ARF with Mdm2 [339], and with p53 in lung tumours [364,366], suggesting that both of them may regulate p14ARF expression in the same pathway. Importantly, the study by Hsu *et. al* also indicated that the poor prognosis of patients with LUAD may have stemmed from the mutually exclusive relationship between p14ARF and p53 aberrations [364].

3.6. Chromosome 10q

3.6.1. PTEN

Phosphate and tensin homolog deleted from chromosome ten (*PTEN*) gene is located on chromosome 10q23 and encodes a lipid phosphatase that dephosphorylates phosphatidylinositol-3,4,5-trisphosphate (PIP_3), the lipid product of phosphoinositide-3 (PI3)-Kinase into PIP_2 [367]. Therefore, PTEN is also known as the antagonist of PI3-Kinase as it opposes its pro-survival activity by inhibiting the PI3K/AKT/mTOR signalling pathway [368]. PTEN protein consists of five domains: an N-terminal phosphatase domain with catalytic activity; a short N-terminal composed by a PIP_2-binding domain (PBD); a C2 domain that mediates membrane binding; a C-terminal tail containing two PEST (Pro, Glu, Ser and Thr) sequences; and a PDZ-interaction motif [369].

Aberrant activation of the PI3K/AKT/mTOR pathway may be primarily attributed to either the GOF mutations and genetic amplification of PI3K, or loss of function of PTEN [370]. Dysregulation of this pathway leads to hyperactivation of their proproliferative downstream effectors which ultimately promote tumourigenesis and cellular transformation [367]. In a study where the implication of PTEN/PIK3CA pathway in the tumourigenesis of SCLC was elucidated, a single allelic inactivation of PTEN in RB- and p53-deleted mice has displayed accelerated tumourigenesis and frequent liver metastasis [371]. On the other hand, bi-allelic inactivation of PTEN promoted adenocarcinoma with neuroendocrine differentiation, providing evidence that PTEN is a vital tumour suppressor gene in lung cancers. PTEN downregulation was also observed in multiple NSCLC cell lines; whereas its upregulation led to G0/G1 cell cycle arrest by suppressing S-phase kinase-associated protein 2 (Skp2) expression and by triggering the caspase-3 apoptotic pathway [372]. In a recent study, PTEN loss resulted in lung cancer cell growth and invasion through overexpression of the oncogene stathmin 1 (STMN1) which is a microtubule destabilizer [373], via the PI3K/AKT pathway [374].

PTEN protein expression is frequently downregulated in over 40% of NSCLC [375,376], which has been shown to result in poor prognosis [377]. In a study, allelic loss at 10q23 occurred in only 19% of NSCLC tumours and promoter hypermethylation in 26% of the tumours, suggesting that the downregulation of PTEN protein expression was not distinctly attributable to genetic or epigenetic alterations and that other regulatory mechanisms may also be involved [378]. In fact, PTEN expression is tightly regulated by multiple regulatory mechanisms. For instance, other than genetic alterations (deletions, insertions, and point mutations), PTEN expression is also regulated at transcriptional level via promoter hypermethylation and transcription factors interaction; at post-transcriptional level through miRNA interference; and at post-translational level by acetylation, ubiquitination, phosphorylation, oxidation, S-nitrosylation, and SUMOylation [367,379].

Contrary to the frequent loss of protein expression, *PTEN* genetic alterations occurred only in approximately 2 −7% of lung cancers [380–382]. A mutational analysis performed using polymerase chain reaction (PCR) and direct sequencing revealed that PTEN mutations occurred predominantly in the catalytic phosphatase domain in NSCLC tumours. Notably, these mutations are also associated with cigarette smoking and LSCC, suggesting that cigarette smoke may be the main driver of mutagenesis [382]. Additionally, EGFR-mutated NSCLCs can also have concurrent PTEN loss, which was associated with shorter PFS and OS, and poor ORR to TKIs compared to PTEN positive tumours [382, 383].

3.7. Chromosome 13q

3.7.1. Retinoblastoma gene

Retinoblastoma (*RB*) gene belongs to the pocket protein family comprising of *RB1* (*p105*), *p107*, and *p130* [384]. It is located on chromosome 13q14 and encodes pRb which consists of the structured N-terminal domain (RbN) and a central pocket domain; disordered primary sequences including loops in RbN (RbNL) and pocket domain (RbPL), an interdomain linker (RbIDL), and a C-terminal domain (RbC) [385]. RB gene is a downstream effector of the p53 pathway which induces G1 cell cycle arrest.

In normal cells, hypophosphorylated pRb maintains cell cycle arrest by binding to E2F transcription factors which are required for G1/S transition [386]. Additionally, pRb can also inhibit cell cycle progression by inhibiting S-phase kinase-associated protein 2 (Skp2)-p27 interaction thereby stabilizing the kinase inhibitor, p27 [387]. Furthermore, pRb also plays a role in regulating apoptosis via its interaction with E2F family members [388]. Particularly, E2F1 but not the other E2F family members (E2F2–5) were shown to induce apoptosis by activating the transcription of $p14^{ARF}$ gene and prevent Mdm2-mediated degradation of p53 [344]. E2F1 also mediates apoptosis by directly activating several pro-apoptotic genes including *APAF1*, Bcl-2 homology 3 (BH3)-only proteins (*PUMA*, *NOXA*, *BIM* , *BIK*, and *Hrk/DP-5*), caspase family members (CASP-2, −3, −7, −8 and −9), and apoptosis-signal-regulating kinase 1 (*ASK1*). Besides, E2F1 can

also inhibit the expression of anti-apoptotic NFκB and Bcl-2 family members, as well as downregulating TNF receptor-associated factor 2 (TRAF2) protein which is needed for NFκB activation [389–392].

pRb phosphorylation and inhibition by CDK4/6–Cyclin D and CDK2-Cyclin E liberate E2F from inhibition, thus allowing S phase entry [393,394]. pRb loss is often observed in SCLC, but it is a rare event in NSCLC [395,396]. Hyperphosphorylation of pRb is mainly due to loss of p16 cyclin-dependent kinase (CDK) or overexpression of cyclins D1 and E. Bi-allelic loss of RB (65%) and TP53 (90%) is frequently encountered in SCLC [22,397,398]. Interestingly, in a study to interrogate the molecular changes that accompany the transition of resistant EGFR mutant NSCLC to SCLC, it was noted that all (100%) the EGFR mutant SCLC transformed samples also exhibited classical SCLC features such as universal loss of *RB* and *EGFR* expressions, and increased sensitivity to Bcl-2 family inhibition. Nonetheless, *RB* knockdown studies had revealed that its loss alone may be insufficient to promote the transformation [399]. Meanwhile, Walter *et. al* reported in their study that the loss of pRb led to tumourigenesis and metastasis; but restoring *RB* gene could suppress metastasis by reverting the tumours into a less aggressive state [400]. Their findings suggested that reactivation of the pRb pathway might be a possible therapeutic strategy for treating tumours with *RB* loss.

3.7.2. Klotho

Klotho (*KL*) gene located on the chromosomal locus 13q12 is an anti-aging gene which encodes a type-1 transmembrane protein consisting of an intracellular domain, a transmembrane domain and an extracellular domain [401]. The extracellular domain of Klotho protein consists of two internal repeats, KL1 and KL2 that can be cleaved and released into the serum as soluble Klothos or undergo alternative mRNA splicing to generate secreted Klothos. Circulating forms of Klotho are thought to have hormonal action and regulate functions in tissues that do not express Klotho [401,402]. Several studies have shown that the down-regulation of *KL* gene expression is associated with tumourigenesis in a variety of cancers, for instance breast [403], lung [404–406], and pancreatic cancers [407].

The tumour suppressive roles of *KL* genes in lung cancer have been well demonstrated in several studies. It decreased cell proliferation and migration by inhibiting the IGF-1/insulin and Wnt -TCF/β-catenin signalling pathways [404,405]; by inducing apoptosis through the bax/bcl-2 pathway [405]; and by suppressing EMT in LSCC [408]. It has also been shown to alleviate resistance to cisplatin-based chemotherapy in lung cancer by modulating the PI3K/Akt signalling pathway [406]. A recent study identified Rab 8 GTPase as a Klotho-interacting protein, where it was shown to regulate the trafficking of Klotho onto cell surface membrane [409]. Overexpression of Rab 8 GTPase was found to increase tumour suppressing effect of *Klotho* gene in NSCLC *in vivo* by retarding Klotho-mediated inhibition of cell proliferation and invasiveness [409].

3.8. Chromosome 17p

3.8.1. TP53

TP53 is located at 17p13 and contains 11 exons which encode a 53 kD nuclear phosphoprotein, p53. TP53 gene is activated in response to cellular stresses, for instance oncogenic activation (*MYC*, *E2F1*, *RAS*, and *BCR-ABL*), hypoxia, and DNA damage [236,410]. The p53 protein encoded by the TP53 gene contains the N-terminal region including a transactivation domain and a proline-rich domain; a hydrophobic core containing DNA-binding domain; and the C-terminal region comprising of a negative regulatory domain along with an oligomerization domain [411].

The well-known tumour suppressor p53 may carry out their anti-tumour function by acting as a transcription factor and binds to downstream target genes, such as *p21*, *MDM2*, *PUMA*, and *BAX*, all of which encode proteins involved in the regulation of cell cycle, differentiation, apoptosis, and DNA repair [412]. It also exerts antiproliferative activity by inducing the intrinsic (mitochondrial-mediated) or extrinsic (death receptor-mediated) apoptosis pathways [413,414]. The p53-dependent intrinsic apoptotic pathway is initiated through p53-mediated transcriptional activation of pro-apoptotic BH3-only members of the Bcl-2 protein family such as PUMA, BID, BAD, BIM, BIK, BMF, HRK, and NOXA. The BH-3 only proteins in turn activate the cell death effector proteins BAX, BAK and BOK which trigger mitochondrial outer membrane permeabilization (MOMP) and ultimately activate the caspase cascade apoptosis [413–415]. On the other hand, the death receptor apoptotic pathway is instigated upon binding of death ligands tumour necrosis factor (TNF), Fas ligand (Fas-L), and TNF-related apoptosis-inducing ligand (TRAIL) to death receptors (TNFR, FAS, and TRAIL receptors), which subsequently will also lead to caspase activation [413,414]. Other than apoptosis induction, p53 also mediates cell-cycle arrest at G1/S mainly through *p21*; and at G2/M through DNA-damage-inducible 45 (*GADD45*), *Reprimo*, and *14–3–3σ* genes [416,417]. Theses cell cycle checkpoint controls are crucial in maintaining genomic stability as they buffer time for DNA repair [418].

Mutations of *TP53* gene (predominantly missense mutations) are found in high frequency in SCLC (70–80%) [419,420], and in lower frequency in NSCLC (about 50%) [420,421]. LSCC has a higher frequency (50–70%) of TP53 mutation compared to LUAD (40%) [420–422]. These mutations occur mostly in exons 4–9 encoding the DNA-binding domain, resulting in the production of non-functional p53 protein lacking the specific DNA-binding activity [423]. As functional p53 is necessary for apoptosis to occur, these mutations could alter the cytotoxic effects of chemotherapy or radiation and confer resistance to these therapies in SCLC and locally advanced NSCLC [424–426]. Mutant p53 can also exert domain-negative effect (DNE) by complexing with other wild-type p53 and inactivate them [427]. On the other hand, GOF mutations result in the production of mutant p53 which can bind with other *TP53* gene family (*p63* and *p73*), hence blocking their transactivation activities [423,428].

GOF p53 mutants have been shown to enhance motility in multiple cancer cell lines by upregulating expressions of CXC chemokines such as CXCL5, CXCL8 and CXCL12 [429]. Additionally, CXCL5 expression was also elevated in majority of the lung tumours harbouring GOF p53 mutants, suggesting that these mutant proteins play a role in tumourigenesis in human cancers [429]. Alternatively, GOF p53 proteins can also upregulate the anti-apoptotic gene *NFκB2* [430], *IGF2* [431], and *TIMM50* [432], as well as suppress the transcription of pro-apoptotic genes, such as *CD95* [433], *TGFR2*, [434], and *caspase 3* [435]. Furthermore, these mutant p53 proteins can also impair cell cycle regulation by interacting with the transcription factor nuclear factor Y (NF-Y) [436], and the transcriptional co-activator YAP [437]. Together, mutant p53 and YAP form a complex with NF-Y thus led to aberrant expression of cyclin A, cyclin B, CDC25C, and CDK1 [438].

Introduction of wild-type p53 gene into p53-decificient lung cancer cells has been shown to induce chemo- and radiosensitivity [439–441]. In contrast, other studies reported negative outcomes, where the combination of gene therapy and chemotherapy was not superior to chemotherapy [442]; and that gene transfer was insufficient to resensitize the cells to chemotherapy [443]. Intriguingly, a study showed that high-energy radiation such as the high linear energy transfer (high-LET) can induce p53-independent cell death, as there was no significant difference in radiosensitivity between wild-type and mutated p53 cells [444]. In light of these observations, Mori *et.* al proposed a model for high- and low-LET radiation-induced apoptosis pathways. In their model, high LET radiation was postulated to trigger caspase-9 and subsequently caspase-3 in a p53-independent manner, which ultimately leads to caspase-mediated apoptosis. In contrast, low LET radiation activates caspase-8 via p53, which then converges into the caspase-9 apoptosis pathway [445]. The p53 apoptosis effect related to PMP-22 (PERP) is a membrane protein and a downstream effector of p53 that has been shown to play a role in p53 stability [446]. A recent study discovered that the *PERP-428CC* and *PERP-428CG* genotypes are more

vulnerable to reactive oxygen species (ROS)-induced DNA damage thus have a higher lung cancer risk than the *PERP-428GG* genotype [447]. This is attributed to the fact that PERP-428 C isoform confers higher stability to p53 which decreases the expression of antioxidant genes. Therefore, individuals with the *PERP-428CC*/CG genotypes have a low antioxidant capacity, which means that antioxidant strategies are of utmost importance in cancer prevention [447].

3.9. Chromosome 19p

3.9.1. STK11

Serine/threonine kinase 11 (*STK11*) gene is located on 19p13.3 and encodes the serine/threonine kinase liver kinase B1 (LKB1). LKB1 consists of an N-terminal domain with a nuclear localisation signal, a central protein kinase domain and C-terminal region where post-translational modifications (phosphorylation and prenylation) take place [448]. LKB1 forms a heterotrimeric complex with the pseudokinase STE20-related adaptor (STRAD) and the scaffolding mouse protein 25 (MO25) and adopts an active conformation which is stabilized via the interaction between MO25 and LKB1 activation loop [449]. AMP-activated protein kinase (AMPK), a key energy sensor and regulator of cellular metabolism is known to be a substrate for LKB1, whereby it is activated via phosphorylation by LKB1 [450].

Activation of AMPK in turn activates its downstream effectors, such as tuberous sclerosis protein 1 and 2 (TSC1/2) which antagonize the mTOR pathway responsible for cell proliferation [451]. Phosphorylation of TSC1/2 inhibits Ras homolog enriched in the brain (Rheb) which is required for the activation of mammalian target of rapamycin complex 1 (mTORC1) [451]. Aside from inducing cell growth [452], mTORC1 also suppresses autophagy by phosphorylating and inhibiting components of the UNC-51 like autophagy activating kinase (ULK) complex such as autophagy related gene 13 (ATG13) and ULK1/2 kinase under energy sufficient state [453]. mTORC1 also phosphorylates ULK1 on Ser 757 to prevent its activation by AMPK, thereby inhibiting autophagy [454]. Under nutrient and energy deprivation state, increased adenosine monophosphate (AMP) to ATP ratio activates AMPK which in turn inactivates mTORC1 directly by phosphorylating RAPTOR protein or indirectly via activating TSC2 and elicits autophagy [455]. Moreover, AMPK can also directly phosphorylate ULK1 on Ser 317 and Ser 777 to activate it [454].

Paradoxically, LKB1 also interacts with other AMPK-related kinases (ARKs) with oncogenic activity such as microtubule affinity-regulating kinase 2 (MARK2), which is frequently overexpressed in NSCLC and has been shown to suppress the anti-apoptotic NFκB pathway leading to cisplatin resistance [456] and promote Warburg effect leading to tumour growth by inhibiting AMPKα1 [457]; and novel (nua) kinase family 1 (NUAK1) or also known as ARK5 which promotes cancer cell survival [458,459], metastasis [460], and is associated with poor prognosis [461] and chemoresistance [462]. Indeed, LKB1 can help maintain cancer cell viability under metabolic stresses by maintaining energy homeostasis, reducing oxidative stress, and by preventing cancer cells from matrix detachment [463]. In the brain, LKB1 also interacts with brain-specific serine/threonine-protein kinase 1 (BRSK1; or SAD-B) that plays a pivotal role in cortical development and neuronal polarization [464,465]. Thus, loss of *STK11* which is a key activator of AMPK, results in deregulation of its aforementioned downstream signalling pathways and in turn drives tumourigenesis in a vast variety of human cancers [466–468].

STK11 genetic mutations are common events in a vast majority of cancers, including NSCLC. Genetic alterations (predominantly non-sense and deletion mutations) of LKB1 are highly prevalent in NSCLC (39%) compared to SCLC (5%), especially LUAD [469]. By utilizing the chromogenic in situ hybridization (CISH) approach, loss of *STK11* gene locus by either LOH (62%) or homozygous deletion (28%) was detected in almost 90% of NSCLCs [470]. LKB1 co-mutation was also particularly enriched in KRAS-mutant LUAD in both early-stage and metastatic cohorts [193]. Additionally, the LKB1/KRAS co-mutant LUAD was more sensitive to HSP90 inhibition and has lower PD-L1 expression [193]. In a cohort of NSCLC patients who received chemotherapy, *STK11* genetic mutation was identified in 8% of the cases and about half of them had concomitant KRAS mutation with an exceptionally bad prognosis [471]. This finding was consistent with other more recent studies [472,473]. Concurrent *STK11/KEAP1* mutation was also shown to downregulate major histocompatibility complex class 2 (MHC-2) gene expression required for the activation of CD4+ T-cell, and genes critical for immune processes (e.g., leukocyte recruitment and inflammatory cytokine production) in KRAS-mutant tumours [474]. Hence, it was not surprising that *STK11/KEAP1* co-mutation could compromise the clinical efficacy of immunotherapy, which rendered the LUAD patients with coexisting *KRAS* mutation having worse clinical outcomes with immunotherapy [474]. These studies therefore suggested that STK11 mutation is a negative prognostic marker rather than a predictive marker for chemotherapy and immunotherapy as both these treatments were linked to poor clinical outcomes in patients harbouring STK11 mutation and other coexisting mutations [475,476].

Previously, it has been demonstrated that KRAS/LKB1 co-mutant NSCLCs have increased dependence on deoxythymidylate kinase (DTYMK) which catalyzes the phosphorylation of thymidine monophosphate (dTMP) to thymidine diphosphate (dTDP) essential for DNA synthesis [477]; the urea cycle enzyme carbamoyl phosphate synthetase 1 (CPS1) required for maintaining the pyrimidine pool for DNA replication [478]; and glutamine-fructose-6-phosphatetransaminase 2 (GFPT2) involved in the hexosamine biosynthesis pathway (HBP) that generates the end product UDP-N-acetylglucosamine (UDP-GlcNAc) [479] with cardinal roles in cancer cell signalling, metabolism, EMT, and pluripotent phenotype [480]. According to a recent study, the co-mutation of KRAS and LKB1 increased the dependency on the enzyme N-acetylglucosamine-phosphate mutase 3 (PGM3), which is likewise controlled by LKB1 downstream in the same pathway as GFPT2 [481]. In the study, a PGM3 inhibitor FR054 was shown to inhibit the co-mutant cell viability, thus suggesting a safer alternative therapeutic strategy for targeting the GFPT2 pathway [481].

3.9.2. KEAP1

Kelch-like ECH associated protein 1 (*KEAP1*) gene is located on 19p13.2 and encodes the Keap1 protein containing three domains: the N-terminal Broad-Complex, Tramtrack and Bric a brac (BTB) domain essential for homodimerization of Keap1 and mediate Cul3 binding; a central intervening region (IVR) which interacts with Cul3 protein in the E3 ligase complex as well as facilitates Nrf2 localization; and the C-terminal domain containing six Kelch repeats which mediate Nrf2 binding [482–484].

KEAP1 interacts with nuclear factor, erythroid 2-related factor 2 (*NRF2*) to regulate the oxidative pathway. Under normal physiologic condition, Nrf2 homeostasis is carried out by Keap1 which is found associated with an E3 ubiquitin ligase complex, by mediating Nrf2 proteasomal degradation [482]. In the presence of oxidative stress, KEAP1 undergoes conformational changes and dissociates from NRF2 which is then translocated to the nucleus and transcriptional activation of downstream antioxidant genes [483]. KEAP1 loss of function results in reduced degradation of NRF2, hence activates the KEAP1/NRF2 pathway. Hyperactivation of this antioxidative pathway significantly decreased ROS levels in KEAP-1 mutant lung cancer cells, which contributed to tumourigenesis [485].

Somatic mutation of KEAP1 was identified in around 17% of LUAD patients [187]. *KEAP1* LOH attributed to predominantly missense mutations was found in about 90% of KEAP1-mutant tumours and was identified as a strong negative prognostic factor [486,487]. Concurrent mutation of *STK11/KEAP1* was reported in 10% of metastatic LUAD patient cohort and was remarkably enriched in high-risk group with a significantly shorter OS of 7.3 months compared to that of 32.8 months in low-risk group [486]. Concomitant loss of STK11/KEAP1 displayed

higher ferroptosis-protective gene expression, rendering the co-mutant LUAD cells to become resistant to ferroptosis cell death [488]. Among the list of ferroptosis-protective genes, aldo-keto-reductase-1 C (*AKR1C*) family genes were upregulated in about 80% of the STK11/KEAP1 co-mutant LUAD tumours, which have been shown to play a role in lung cancer cell metastasis [489] and suppression of ferroptosis [490]. Besides, stearoyl-CoA desaturase-1 (SCD1) was also differentially upregulated in STK11/KEAP1 co-mutants, and its expression was essential for the cancer cell survival [488]. Based on these findings, they also evaluated the efficacy of SCD1 inhibitors as a therapeutic candidate for STK11/KEAP11 co-mutant LUAD patients in their study.

In a previous study, *KEAP1* mutation was shown to co-occur in roughly 30% of LUAD tumours harbouring *KRAS* mutation, and it has been linked to a shorter survival time with chemotherapy or immunotherapy [491]. Using the CRISPR-Cas9 system, Romero and colleagues found out that *SLC1A5* gene (encoding a glutamine transporter) was depleted in KEAP-1 mutant cells, suggesting their metabolic dependency on glutaminolysis [211]. This study also showed that glutaminase inhibition effectively suppressed tumour growth *in vivo*, suggesting that glutaminase could be a therapeutic target in KEAP1-mutant LUAD.

3.10. Long Non-coding RNAs

Non-coding RNAs (ncRNAs) are RNAs that do not encode proteins [492]. They can be categorized into housekeeping ncRNAs and regulatory ncRNAs. Housekeeping ncRNAs include transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs). On the other hand, regulatory ncRNAs are classified into two groups based on their size: small ncRNAs and lncRNAs which are shorter and longer than 200 nucleotides, respectively. Small ncRNAs can be further divided into microRNAs, small nucleolar RNAs (snoRNAs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), and PIWI-interacting RNAs (piRNAs) [492].

Long non-coding RNAs (lncRNAs) are non-protein-coding RNA transcripts longer than 200 nucleotides [493]. They are categorized based on their genomic location relative to the protein-coding gene into sense, antisense, bidirectional, intron, intergenic, and enhancer lncRNA [493]. LncRNAs can regulate gene expression at the epigenetic level by interacting with SWI/SNF complexes and DNA methyltransferases for chromosome remodelling [494]; at transcriptional level through their interaction with chromatin at the transcription site and regulatory elements, as well as through chromatin looping [495]; and at post-transcriptional level by binding to RNA-binding proteins or proteins of the signalling pathways, by base pairing with RNAs, and by sponging microRNAs through competitive binding [495]. At post-transcriptional level, lncRNAs act as competing endogenous RNAs (ceRNAs) to competitively bind with microRNAs and antagonize their functions, hence they are also known as microRNA sponges [496,497].

Some lncRNA may function bidirectionally as an oncogene or tumour suppressor gene in a tissue-specific manner [498]. For instance, Taurine Upregulated Gene 1 (TUG1) may exhibit oncogenic function in osteosarcoma [499] and SCLC [500], but its upregulation was associated with better prognosis in NSCLC patients [501]. Some of the identified oncogenic lncRNA in lung cancer include HOTAIR, ANRIL, MALAT1, and H19. On the other hand, several well-characterized tumour suppressive lncRNAs include MEG3, PANDAR BANCR, and GAS5 [502].

3.10.1. MEG

Maternally expressed gene 3 (MEG3) is located on chromosome 14q32.3 and encodes lncRNA MEG3 [503]. It is expressed in normal tissues, but its expression is lost in various types of tumours such as nonfunctioning pituitary tumours [504], gastric cancer [505], and prostate cancer [506], suggesting its cardinal tumour suppressive role in cancers. Overexpression of MEG3 has been demonstrated to activate p53 and its target gene, growth differentiation factor 15 (*GDF15*) possibly by inhibiting Mdm2-mediated degradation of p53 [507]. Notably, lncRNA MEG3 also induced growth arrest in p53-null colon cancer cells, indicating that it also functions independently of p53 [507].

A recent study has shown that lncRNA MEG3 negatively regulated dyskeratosis congenita 1 (DKC1) protein, which inhibited lung cancer cell proliferation, migration, and telomerase activity [508]. *DKC1* encodes the dyskerin protein which is required for maintaining telomerase activity [509] and is often upregulated in various cancers [510,511]. DKC1 overexpression has been found to promote telomere lengthening [512], and serves as a negative prognostic factor in lung cancers [513,514]. Other than that, lncRNA MEG3 also acted as ceRNA of miR-7–5p to regulate *BRCA1* expression and enhanced the expression of proapoptotic protein Bax in NSCLC cells [515]. It was demonstrated that it suppressed NSCLC cell migration by sponging miR-21–5p, which led to PTEN upregulation and subsequent inhibition of the PI3K/AKT pathway [516].

A study also stipulated that overexpression of lncRNA MEG3 resulted in decreased autophagic activity in lung cancer cells, which in turn led to enhanced sensitivity to chemotherapy (vincristine) [517]. Emerging evidence has shown that autophagy may cause resistance to cancer therapy by blocking apoptosis through ATM-induced DNA damage repair [518]; maintaining the stemness of CSCs [519,520]; and eliminating ROS generated from the cytotoxic therapy [521]. LncRNA MEG3 was shown to implicate the autophagy activity by regulating the miR-543/indoleamine-pyrrole 2,3-dioxygenase (IDO) signalling pathway, which suggested the potential therapeutic utility of IDO inhibitor in NSCLC treatment [522]. Previously, a study identified a novel mechanism by which pRb could increase MEG3 expression by downregulating DNA methyltransferase 1 (DNMT1), and suggested palbociclib, a CDK4/6 inhibitor as a potential treatment for NSCLC [523].

3.10.2. PANDAR

Promoter of CDKN1A antisense DNA damage activated RNA (*PANDAR*) is mapped onto chromosome 6p21.2 and is located upstream of the *CDKN1A* transcriptional start site. As its name suggests, it is co-activated with CDKN1A by p53 in response to DNA damage or oncogenic stimuli [524]. Once activated by p53 upon DNA damage, it encodes the lncRNA PANDAR which interacts with nuclear transcription factor Y subunit alpha (NF-YA) and abrogates the activation of proapoptotic genes, thus promoting cell survival [524]. PANDAR is recognized as a unique lncRNA due to its contradictory roles as both an oncogene and a tumour suppressor gene in different types of cancer [502].

While it was often overexpressed in most human malignancies such as colorectal, bladder, and breast cancers [502], its expression was consistently low in lung cancer [525,526], highlighting that lncRNA PANDAR is functionally distinct in a tissue-specific manner. In colorectal cancer, PANDAR overexpression was a negative prognostic marker and was shown to promote metastasis by upregulating EMT-associated genes [527]; whereas in breast cancer, PANDAR was upregulated and silencing its gene expression suppressed $p16^{INK4a}$ and inhibited G1/S transition [528]. On the other hand, the tumour suppressive role of PANDAR in lung cancer was identified in the study by Zhang *et. al* where they discovered a correlation between the expressions of lncRNA PANDAR and the autophagy regulator beclin 1 (*BECN1*) [526]. Additionally, they also reported that PANDAR could also enhance apoptosis in NSCLC cells [526]. These findings were in line with a previous study, in which lncRNA PANDAR has been shown to induce caspase-3-mediated apoptosis by regulating Bcl-2 and that low expression was a predictor of bad prognosis in NSCLC [525]. Furthermore, Bcl-2 was also known to interact with beclin1 protein to regulate autophagy [529]. In aggregate, these results indicate that lncRNA PANDAR functions as a tumour suppressor in lung cancer by regulating type I and type II cell death.

3.10.3. GAS5

Growth arrest-special transcript 5 (*GAS5*) is mapped onto chromosome 1q25.1 and has a sequence structure that resembles a typical protein-coding gene, with 12 exons and 11 introns, but it does not encode a protein [530]. It undergoes alternative splicing to generate two

lncRNAs, known as GAS5a and GAS5b [530]. An increasing body of evidence has underscored the tumour suppressive role of GAS5 in various human carcinomas, including lung cancer, gastric cancer, hepatocellular carcinoma, and renal cancer [530]. It exerts its biological effects via several key mechanisms. Firstly, it acts as a ceRNA to sequester miRNAs and prevents their association with their target mRNAs and indirectly influencing the expression of genes involved in cell growth and survival [530]. Secondly, it also functions as a molecular sponge for the glucocorticoid receptor (GR), inhibiting GR activity and its interaction with glucocorticoid response elements (GREs) [530]. A notable example of Gas5's modulation of the GR pathway is the repression of glucocorticoid-responsive antiapoptotic genes, such as cIAP2 and SGK1, contributing to the sensitization of cells to apoptosis [531]. Additionally, GAS5 can directly bind to target mRNAs to regulate target gene translation and impact protein expression levels [530].

GAS5 expression was downregulated in lung cancer tissues compared to the adjacent normal lung tissues and was correlated with tumour differentiation, TNM stage and lymph node metastasis [532–534]. In lung cancer cells, overexpression of GAS5 induced cancer cell apoptosis [532,535], inhibited the migration and invasion activities [535–538]. In vivo studies revealed that GAS5 suppressed tumour growth and metastasis [532,535,538]. The tumour suppressive activities of GAS5 in limiting tumourigenesis, migration, and invasion are via p53-dependent and p53-independent (E2F1) pathways [532], EMT pathway (E-cadherin and N-cadherin) [535], miR-205/PTEN axis [536], miR-217/LHPP axis [538] and the miR-221–3p/IRF2 axis [537]. Additionally, GAS5 has been shown to enhance sensitivity of lung cancer cells to EGFR-TKI gefitinib [534] and cisplatin [538] by targeting IGF-1R and the miR-217/LHPP axis, respectively.

3.10.4. Novel tumour suppressive lncRNAs

It was recently discovered that lung cancer tissues have significantly lower levels of the lncRNA PGM5P4-AS1 compared to normal tissues [539]. Accordingly, overexpression of PGM5P4-AS1 inhibited lung cancer cell proliferation, migration, and invasiveness in vitro, and suppressed tumour growth in vivo [539]. They act as miRNA sponge for miR-1275, which is a negative regulator of leucine zipper putative tumour suppressor 3 (LZTS3) and is associated with cancer cell proliferation and migration [539]. In another study, keratin-7 antisense (KRT7-AS) was downregulated in lung cancers, whereas its overexpression significantly suppressed tumour growth in vivo in both lung and breast cancers [540]. Furthermore, KRT7-AS-expressing cancer cells exhibited increased cisplatin sensitivity and enhanced cisplatin-induced cell death [540]. The tumour suppressive function of KRT7-AS is closely linked to its ability to bind to the core nucleic acid motif of PTEN protein and protect it from ubiquitination-proteasomal degradation, thereby upregulating its expression [540]. Additionally, they discovered that RXRα is the primary transcription factor that drives KRT7-AS transcription. This suggests that berberine, an RXRα agonist, may be useful in boosting KRT7-AS transcription and its tumour suppressive properties [540]. Importantly, KRT7-AS reduced Keratin-7 levels [540], which is frequently implicated in a wide array of human malignancies, and whose overexpression is often associated with tumour growth, cancer cell invasion, increased drug resistance and poor prognosis [540].

In a recent study, a novel tumour suppressive lncRNA, termed TP53-inhibiting lncRNA (TILR), was found to function as a constitutive negative regulator of p53 expression, leading to downstream effects on genes involved in cell cycle regulation (p21 and MDM2) and apoptosis in lung cancer [541]. The study also unveiled the interaction between TILR and Poly(rC)-binding protein 2 (PCBP2), and it was discovered that the mid-portion of TILR is crucial for binding to both PCBP2 and p53 mRNA [541]. Depletion of PCBP2 resulted in effects similar to TILR silencing, suggesting that TILR's regulatory function is closely linked to its association with PCBP2. Notably, TILR was identified as a component of a positive feedback loop involving the Fanconi anaemia pathway genes and p53, contributing to the maintenance of low levels of p53 transcriptional activity. Together, these findings suggest that TILR works in conjunction with PCBP2 to fine-tune p53 expression to prevent unwarranted apoptosis, shedding light onto the intricate regulatory mechanisms associated with lung cancer development. [541].

3.11. MicroRNAs

MicroRNAs are single-stranded, non-coding RNAs of 19–25 nucleotides in length that regulate gene expression by binding to 3'untranslated regions (3'UTRs) of the target genes and interfere with mRNA translation or promote mRNA degradation [542]. miRNAs can be oncogenic or tumour suppressive in nature depending on the tumour type and the regulatory function of the implicated target genes [542]. On one hand, the oncogenic miRNAs (oncomiRs) such as miR-17–92 cluster, miR-21, miR-31, and miR-224 are often upregulated in lung cancer. On the other hand, some of the representative tumour-suppressing miRNAs (TS miRNAs) including let-7, miR-34, miR-17/92, miR-200 are frequently downregulated [543]. In recent years, miRNAs have gained interest from researchers due to mounting evidence that proves them to be at the heart of cancer development owing to their multifaceted roles in regulating the expressions of multiple genes [544]. Therapeutic targeting of miRNAs associated with cancer progression thus emerged as a research hot spot and prompted the discovery of miRNAs involved in various human malignancies, including lung cancer (see Table 2).

3.11.1. Let-7

In humans, the Lethal-7 *(let-7)* family comprises of 12 family members: *let-7a-1*,*7a-2*, *7a-3*, *7b*, *7c*, *7d*, *7e*, *f7–1*, *7 f-2*, *7 g*, *7i*, and miR-98 spanning eight genomic loci [545]. The human *let-7 (hsa-let-7)* may be encoded individually (*let-7 g* and *let-7i*) or in clusters with other miRNAs (e.g., *let-7c*, *miR-99a*, and *miR-125b-2*) [546]. In mammals, *let-7* miRNAs have been shown to play a fundamental role during embryogenesis as well as in regulating haematopoietic stem cell homeostasis and the differentiation of cells of the immune system such as CD8 and NKT cells [546–549].

The mammalian LIN28 family comprises of two members, *LIN28A* and *LIN28B*, each encoding a highly conserved RNA-binding protein (RBP) [550]. The RBPs consist of a cold-shock domain and two CysCysHisCys (CCHC) zinc finger domains that can bind to pre-let-7 and recruit Terminal Uridylyl Transferase 4 (TUT 4) to polyuridylate 3'end of the precursor and inhibit miRNA biogenesis. *LIN28* and *let-7* can regulate each other's expression in a double negative feedback manner [551], therefore uncoordinated expression of either gene may contribute to cancer development. In fact, overexpression of *LIN28* has been reported in a number of cancers with coexisting low *let-7* expression and resulted in bad prognosis [552–554].

Several lines of evidence indicated that *let-7* is an important tumour suppressor as it was often downregulated across several human cancers [555]. The clinical significance of *let-7* downregulation in human lung cancer was first demonstrated by a group of Japanese researchers, in which they reported that reduction of *let-7* expression resulted in poor prognosis after curative resection [556]. A study revealed that *let-7* was negatively related with *RAS* expression in tumour samples [557], implicating that it has tumour suppressive function by inhibiting the proto-oncogene RAS, which is a significant upstream regulator of the PI3K, Ral, and Raf signalling cascades [558]. Its function as a tumour suppressor was also evident in another study conducted by Kumar and colleagues where *let-7 g*, a *let-7* family member was shown to suppress KRAS and NRAS in NCSLC and attenuated tumourigenesis [559]. Other than that, *let-7* family members were also shown to inhibit cell cycle progression by repressing the cell-cycle progression regulators such as CDK4, CDK6, CDC25A, and cyclins A, D1, and D3 [222,560,561]. Furthermore, it was demonstrated that *let-7b* and *MYC* gene also regulate each other in a double negative-feedback manner [562].

A study showed that *let-7* can also suppress PD-L1 expression via

Table 2
Tumour suppressor microRNAs with their target gene(s) and the relevant cancer associated mechanisms in lung cancer.

Tumour suppressor microRNA	Target	Implicated cancer associated mechanism		Underlying mechanisms/ Clinical significance	Ref.
miR-183–5p	PIK3CA	(+)	G1 cell cycle arrest Apoptosis	CyclinD1, matrix metalloproteinases 2 and 9 (MMP2 and MMP9) were also downregulated along with suppression of AKT pathway.	[630]
		(-)	Cell proliferation Migration & invasion		
miR-501–3p	RAP1A	(-)	Cell proliferation Migration & invasion	LSCC patients with low expression of miR-501–3p has shorter OS compared with those with high expression.	[631]
miR-520c-3p	AKT1 & AKT2	(+)	S phase & G2 cell cycle arrest Apoptosis	AKT1 and AKT2 are downregulated by DNA methylation and upregulated by transcription factor Yin Yang 1 (YY1) upstream.	[632]
		(-)	Cell proliferation Migration & invasion		
miR-186	Dicer1	(-)	Cell proliferation Migration & invasion	miR-186 expression is negatively correlated with Dicer1 expression which is associated with TNM stage and lymph node metastasis.	[633]
miR-188	MAP3K3	(+)	Apoptosis	miR-188 delivery is superior to MAP3K3 knockdown in suppressing tumour growth, suggesting that miR-188 may regulate other pathways in tumour suppression which have not been elucidated.	[634]
		(-)	Cell proliferation Migration & invasion		
miR-886–3p	TGF-ß1	(+)	Mesenchymal-epithelial transition	Intratumor and intravenous administration of exogenous miR-886–3p mimic suppressed tumour invasion, suggesting that local or systemic delivery of miR-886–3p may provide clinical benefits in SCLC treatment.	[635]
		(-)	Cell proliferation Migration & invasion		
MiR-641	MDM2	(+)	Apoptosis	Overexpression of miR-641 decreased MDM2 expression while increasing p53 expression.	[636]
		(-)	Cell proliferation		
miR-155–5p	SMAD2/3	(-)	Cell proliferation Migration & invasion	miR-155–5p significantly suppressed the Smad2/ZEB signalling pathway.	[637]
miR-218	IL-6R & JAK3	(-)	Cell proliferation Migration & invasion	miR-218 negatively regulates the IL-6/JAK/STAT3 pathway.	[638]
MiR-125b-1–3-p	S1PR1	(+)	Apoptosis	miR-125b-1–3p may regulate the STAT3 signalling through phosphorylation.	[639]
		(-)	Cell proliferation Migration & invasion		
miR-223–3p	p53	(-)	Cell proliferation Migration & invasion	miR-223–3p is regulated by mutant p53 in a negative feedback loop at transcriptional level.	[640]
miR-519a	STAT3	(-)	Cell proliferation Migration & invasion	Low expression of miR-519a is associated with poor prognosis.	[641]
miR-557	LEF1	(-)	Cell proliferation Migration & invasion	Induction of cell death by miR-557 is not by apoptosis.	[642]
miR-29a	NRAS	(-)	Cell proliferation	Overexpression of miR-29a led to increased sensitivity of lung cancer cells to cisplatin.	[643]
miR-7–5p	NOVA2	(-)	Cell proliferation Migration & invasion	Low expression of miR-7–5p is associated with poor prognosis.	[644]
miR-138	YAP1	(-)	Cell proliferation Migration & invasion	miR-138 mediated inhibition of migration and invasion is independent of YAP1.	[645]
miR-486–5p	CDK4	(+)	G1 cell cycle arrest Apoptosis	Expression downregulation is due to hypermethylation of the promoter region of miR-486–5p in tumour tissues.	[646]
		(-)	Cell proliferation		
miR-137	SLC22A18	(-)	Cell proliferation Migration & invasion	Low expression of miR-137 is associated with high TNM stage and poor prognosis.	[647]
miR-9–1	UHRF1	(+)	G1 cell cycle arrest Apoptosis	Tumour suppressor genes p15, p16, and p21 are also reactivated due to UHRF1 inhibition.	[648]
		(-)	Cell proliferation		
miR-329	MET	(+)	Apoptosis	miR-329 increases p57 and p21 expressions while inhibiting expressions of cyclin D1/2 and MMP7/9.	[649]
		(-)	Cell proliferation Migration & invasion		
miR-133-a	LASP1	(-)	Cell proliferation	TGF-β/Smad3 signalling pathway is suppressed by miR-133-a.	[650]
miR-145 & miR-497	MTDH	(-)	Migration & invasion	TGF-β-induced EMT is suppressed by miR-145 & miR-497.	[651]

(+) indicates induction; (-) indicates inhibition; OS: overall survival; TNM: tumour, node, metastasis.

post-translational modification in MCF-7, U2OS, and Hela cells. In the study, they also found out that C1632, a LIN28 inhibitor was able to reduce PD-L1 expression and cell growth both *in vitro* and *in vivo* [563]. Let-7 also negatively regulates high mobility group protein A2 (HMGA2) [564], a non-histone transcription factor that indirectly regulates gene transcription by binding to and altering DNA structure [565]; and signal transducer and activator of transcription 3 (STAT3) [566] in the JAK-STAT signalling cascade that is often activated in cancers [567].

Let-7a was shown to upregulate the expression of proapoptotic Bax and cleaved caspase-3, −8 and −9, while downregulating the anti-apoptotic Bcl-2 protein in LUAD cell lines [560]. In a study, restoring *let-7b* expression was shown to downregulate KRAS and increase sensitivity to chemotherapeutic drugs in NSCLC, which led to cell cycle arrest and tumour invasion [568]. *Let-7c* plays a role in suppressing metastasis in NSCLC by decreasing the expressions of integrin subunit beta 3 (ITGB3), an integrin family member; and mitogen-activated protein kinase kinase kinase kinase 3 (MAP4K3) [569], which regulates the mTOR, EGFR, and JNK pathways [570,571]. Furthermore, a meta-analysis suggested that low *let-7* expression often occurred in NSCLC and was significantly correlated with poor prognosis [572].

3.11.2. *miR-34 family*

The miR-34 is a family of three members: *miR-34a* located on chromosome 1p36.22; miR-34b and miR-34c located on chromosome 11q23.1 [573]. The miR-34a is highly expressed in most tissues except the lung, whereas miR-34b and mir-34c are expressed predominantly in lung tissues [574]. miR-34 family members are regulated differently due to their different genomic loci [573]. The miR-34 gene transcription is directly induced by *TP53* gene in response to DNA damage and oncogenic stress to regulate cell cycle, differentiation, migration, stemness

and survival [575]. Other than that, miR-34 expression is also regulated epigenetically via promoter methylation; by other p53 family members (p63 and p73); and by EMT-inducing transcription factors such as zinc-finger E-box-binding homeobox 1 (ZEB1) and snail family transcriptional repressor 1 (SNAIL) [576].

Although the miR-34 family members have similar seed sequences [573,577], a growing body of evidence has showed that each family member has distinct functions and effects on tumour suppression. For instance, a study showed that miR-34b/c were more potent tumour suppressors compared to miR-34a in terms of EMT inhibition in NSCLC [577]. In NSCLC, miR-34a was shown to exert antitumour effect by downregulating NOTCH1 and its downstream target genes *cyclin D1*, hairy and enhancer of split-1 *(HES-1)*, *BCL-2* and *Survivin* [578]; transforming growth factor-β receptor type II (*TGFβR2*) [579] which was identified as a significant negative prognostic marker even in patients treated with chemotherapy [580]; and platelet-derived growth factor receptor alpha and beta (*PDGFR-α/β*) which resulted in TRAIL-induced apoptosis and reduced cancer cell migration [581]. Furthermore, miRNA target prediction tool also revealed binding sites of miR-34a and miR-497 on the 3' UTR region of cyclin E1 (*CCNE1*), implying that both of them may act in concert to control cell growth by regulating *CCNE1* expression [582].

CDK4 has been identified as a direct target of miR-34b-3p and high expression of miR-34b-3p has been shown to induce cell cycle arrest and apoptosis in NSCLC [583]. Other than that, the oncogenes involved in SCLC tumourigenesis (*TOP2A*, *MELK*, *CENPF*) were also identified as candidate targets of miR-34b-3p [584]. DNA topoisomerase II alpha (*TOP2A*) encodes a DNA topoisomerase that controls DNA topologic states during transcription and its aberrant expression was associated with worse prognosis in NSCLC [585]. Maternal embryonic leucine zipper kinase (*MELK*) is a serine-threonine kinase of the snf1/AMPK family that plays important roles in cell proliferation, survival, and CSC maintenance, and was shown to drive SCLC oncogenesis through the activation of PI3K/Akt/mTOR pathway by forkhead box M1 (FoxM1) [586,587]. Centromere protein F (*CENPF*) encodes the CENPF protein which associates with the centromere-kinetochore complex essential for chromosome segregation during mitosis and was shown to cooperate with FoxM1 and ERβ2/5 in lung cancer development [588–590]. On the other hand, miR-34c was found out to be lowly expressed in NSCLC and its expression was inversely correlated with PACAP-specific receptor (*PAC1*) [591], which was shown to regulate the transactivation of EGFR located upstream of MAPK and PI3K signalling cascades in lung cancer [592]. A study also found out that the miR-34 family members have a binding site on 3' UTR of *PD-L1*, and they were able to suppress PD-L1 and tumour growth downstream of p53 [593]. Apart from that, the MET proto-oncogene, receptor tyrosine kinase (*MET*) gene which is also involved in the tumourigenesis of lung cancer is also negatively regulated by the miR-34 family members [594].

It was reported that miR-34a expression was decreased only in high grade, metastatic LSCC tumours, whereas miR-34b/c level was low regardless of tumour stages or metastasis status [595]. The miR-34 family members were shown to inhibit cell proliferation and migration by suppressing the Notch1 pathway, but miR-34b/c particularly demonstrated stronger inhibition on tumour growth. Specifically, miR-34a was shown to inhibit CD44 highly expressed by CSC, implying that miR-34a plays a significant role in suppressing LSCC tumour metastasis by targeting CD44. This may also explain the finding whereby its expression was more significantly reduced than miR-34b/c in recurred LSCC tumours [595].

Intriguingly, the expression status of miR-34a and miR-34b/c was reversed in LUAD, in which the level of the later was significantly lower in metastatic tumours and was significantly related to distant metastases [596]. In the study, promoter hypermethylation of miR-34a and miR-34b/c was more frequent in LUAD tumours compared to normal lung tissues, but there was no association between methylation status and formation of distant metastases [596]. However, they did find out that the methylation levels and expressions of miR-34 family members were negatively correlated with each other in metastatic cases [596]. This finding confounded a study reporting that there was no association between miR-34b/c methylation status and expression [597], suggesting that other mechanisms other than promoter methylation are involved in the silencing of miR-34, for instance p53 mutations, DNA copy number variation (CNV), and deletion mutations on the chromosomal loci encoding the miRNAs [597,598].

Tanaka and colleagues reported that methylation of miR-34b/c occurred at higher frequency (67%) in SCLC compared to NSCLC (26%), and that among the SCLC cell lines and clinical samples, miR-34b/c was also more frequently methylated than miR-34a [599], which may be attributed to the fact that miR-34b/c functions mainly in lung tissues [573,574]. On the other hand, it was previously reported that miR-34b/c hypermethylation conferred higher rate of recurrence in stage I NSCLC that received curative surgical resection [597], and was also associated with shorter OS and DFS, which were consistent with other existing studies [600,601]. However, it is important to note that these findings have not been consistent since an earlier study indicated that low miR-34a but not miR-34b/c expression was predictive of recurrence in resected NSCLC tumours [598] or some later studies stating that there was no correlation between the methylation frequencies of miR-34 family members and metastasis status [596,602]. These discrepancies may have arisen as a result of small sample sizes (only 72 NSCLC tumour samples were analysed in the study by Lan *et. al*) and difference in tumour stages (20% of grade 3 NSCLC samples were included in the study by Gallardo *et. al* whereas only stage I NSCLC samples were analysed in the study by Wang *et.al*) [597,598,602]. All in all, it can be concluded that miR-34 family members are often downregulated in both SCLC and NSCLC, and that CpG island hypermethylation may play a part in it [596,599]. Additionally, miR-34b/c may exert stronger antitumour effect as it is found at higher concentration in lung tissues, whereas miR-34a may emerge as a prognostic marker for relapse in postoperative lung cancer patients [595,596].

3.11.3. *miR-200 family*

The miR-200 family includes a total of five members: miR-200a, miR-200b, miR-200c, miR-141 and miR-429. miR-200a, miR-200b, and miR-429 are located on the chromosomal locus 1p36, whereas miR-200c and miR-141 on the chromosome 12p13 [603]. Those two clusters are differently expressed and their effects on EMT may depend among tumour types. For instance, in an insulinoma mouse model, it was shown that all the miR-200 family members, except miR-141 were responsible for EMT regulation through *ZEB1* activation [603]. Similarly, in LUAD, *miR-200c* and *miR-141* overexpression was both associated with shorter OS, but miR-200c mainly governed mesenchymal-epithelial transition (MET), whereas miR-141 was responsible for angiogenesis [604].

Nevertheless, substantial number of studies have outlined the tumour suppressive roles of miR-200 family in lung cancer. In a study, miR-200 family members displayed significant downregulation in mouse models of human metastatic LUAD [605]. Furthermore, suppression of miR-200 increased cancer associated fibroblasts (CAFs) proliferation in the TME, as well as activated the Notch signalling pathway by increasing jagged canonical Notch ligand 1 and 2 (Jag1/2) expression which enhanced cancer cell metastasis [605]. Furthermore, miR-200 family was able to control tumour metastasis via immunosuppression by regulating PD-L1 expression [606]. Evidently, ectopic miR-200 expression and ZEB1 suppression were demonstrated to downregulate PD-L1, which raised the amount of infiltrating CD8 TILs, decreased tumour burden, and prevented metastasis. [606]. It was reported that miR-200b expression was low in numerous lung cancer cell lines and tumour specimens [607]. In their study, low miR-200b expression exhibited a negative correlation with PD-L1 expression, indicating that it could possibly serve as a biomarker for PD-L1 expression and a predictor of immunotherapy effectiveness in lung

cancer patients [607]. By utilising the chromatin immunoprecipitation (ChIP) assay, it was revealed that miR-200b can directly target E2F transcription factor 3 isoform b (*E2F3b*) and downregulate its expression, which could retard cancer cell proliferation and reverse resistance to docetaxel treatment in LUAD patients [608,609].

Roybal and colleagues identified two binding sites of miR-200 on the 3'UTR of fms-related receptor tyrosine kinase 1 (*Flt1*) gene by genome scanning and experimental validation [610]. They demonstrated that miR-200 can suppress vascular endothelial growth factor receptor 1 (VEGFR1) expression by targeting *Flt1* gene, and inhibited LUAD cell invasion and metastasis. VEGFR1 encoded by the *Flt1* gene plays a cardinal role in tumour angiogenesis, cell proliferation, survival, and is associated with poor prognosis in lung cancer patients [610,611]. Besides, miR-200b also exerted antiangiogenic effect by silencing the angiogenic ETS proto-oncogene 1, transcription factor (*Ets-1*) gene [612] that is found to induce EMT by binding to and promoting twist family bHLH transcription factor 1 (*TWIST1*) transcription in lung cancer [613]. Additionally, miR-200 family has also been shown to decrease angiogenesis by regulating the expressions of proangiogenic cytokines IL-8 and CXCL1 in several cancer types, including lung cancer [614]. Ubiquitin specific peptidase 25 (*USP25*) was identified as a target gene of miR-200c, and its expression was shown to induce NSCLC cell invasion *in vitro* and metastasis *in vivo* through knock-down experiments [615]. However, overexpression of miR-200c decreased USP25 protein level and was shown to inhibit metastasis and invasion [615]. It has been demonstrated that miR-200c can suppress EMT in NSCLC cells by attenuating the protein expression of high-mobility group box 1 (HMGB1) [616], which assumes a role in promoting EMT by upregulating matrix metalloproteinases (MMPs) expression [617], cancer progression [618], and conferring chemotherapy resistance in lung cancer [619].

3.11.4. *miR-99 family*

The miR-99 family members are miR-99a, miR-99b, and miR-100 located on chromosomes 21, 19, and 11, respectively. miR-100 and miR-99a form clusters with let-7 and miR-125 families within MIR100HG and MIR99AHG, respectively [620]. The miR-99 family members may act as oncomiRs or TS miRNAs in different types of cancer. For instance, miR-99 family members can promote leukemic stem cells (LSCs) self-renewal in acute myeloid leukaemia (AML) by suppressing cell differentiation [621], but also suppress tumour growth in lung cancer [622], colorectal cancer [623], and glioma [624].

In NSCLC, miR-99a expression was shown to repress EMT and stemness by targeting and inhibiting E2F transcription factor 2 (*E2F2*), and EGF-like module-containing, mucin-like, hormone receptor-like 2 (EMR2) [625]. In addition, studies have shown that miR-99a inhibited proliferation, migration, and invasion of lung cancers by targeting the IGF1R [622], AKT1 [622], and NADPH oxidase 4 (NOX4) [626] signalling pathways. Activation of AKT1 results in transcription activation of the downstream gene, matrix metalloproteinase-2 (*MMP-2*) which mediates the degradation of extracellular matrix (ECM), as well as induces tumour invasion and metastasis [622]. On the other hand, NOX4 regulates cell migration and invasion by producing ROS which is required for the activation of PI3K/Akt pathway [626]. Downregulation of miR-99a, which occurred mainly due to histone arginine methylation at the promoter region is associated with lymph node metastasis, shorter PFS and OS in LUAD [627]. This work demonstrated that miR-99a can directly target mTOR to reduce mTOR expression and induce apoptosis, hence the miR-99a expression was also inversely correlated with mTOR expression in LUAD [627]. These results were in line with previous research showing how miR-99a affects cancer cell proliferation by specifically targeting mTOR signalling [628,629].

4. Conclusion

Herein, we have summarized some of the commonly inactivated tumour suppressor genes in lung cancer by various mechanisms such as DNA hypermethylation, miRNA silencing, loss of heterozygosity, and somatic mutations; and unveiled the cardinal role of the relevant tumour suppressor genes in the development of lung cancer. As such, a clear understanding of the regulatory roles of tumour suppressor genes is important for the development of novel diagnostic tools and therapeutic strategies at the molecular level in the near future. In the recent years, therapeutic targeting of tumour suppressor genes emerged as an attractive alternative treatment strategy. However, the limited drug delivery efficacy in gene replacement therapy and the complex feedback networks of the implicated signal transduction pathway [652]; as well as the fact that they are "non-druggable" because they are not a protein kinase or cell surface receptors [653], have long been a major roadblock of the clinical application of these pharmacologic inactivation strategies. Therefore, future studies should be extensively focused on correcting these shortcomings, so that the implicated tumour suppressor genes in lung cancer (as well as in other human cancers) treatment can be effectively exploited. In truth, scientists have already made promising strides with the advancements in CRISPR/Cas9 genome editing system [207] and nanoparticle-based gene delivery system [654]; as well as with the emergence of novel therapeutic strategies such as synthetic lethality approach and collateral vulnerability targeting [652] in therapeutic targeting of tumour suppressor genes.

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CRediT authorship contribution statement

Shaik Afzal B.: Writing – original draft, Methodology. **Saktivel Lakshmana Prabu:** Writing – original draft. **Gupta Gaurav:** Writing – original draft. **Negi Poonam:** Writing – original draft. **Barakat Muna:** Writing – original draft. **Singh Sachin Kumar:** Writing – original draft, Data curation. **Dua Kamal:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Data curation. **Chellappan Dinesh Kumar:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Lee Jia Yee:** Writing – original draft, Resources. **Bhandare Richie R.:** Writing – review & editing, Funding acquisition, Conceptualization. **Boddu Sai H.S.:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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