Review article

The crosstalk between non-coding RNA polymorphisms and resistance to lung cancer therapies

Samaneh Mollazadeh [a], Negar Abdolahzadeh [b], Meysam Moghbeli [c], Fatemeh Arab [c,**], Ehsan Saburi [c,d,*]

[a] Natural Products and Medicinal Plants Research Center, North Khorasan University of Medical Sciences, Bojnurd, Iran
[b] Department of Advanced Sciences and Technologies, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran
[c] Medical Genetics and Molecular Medicine Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[d] Medical Genetics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

ABSTRACT

Lung cancer (LC) is one of the most common cancer-related mortality in the world. Even with intensive multimodality therapies, lung cancer has a poor prognosis and a high morbidity rate. This review focused on the role of non-coding RNA polymorphisms such as lncRNAs and miRNAs in the resistance to LC therapies, which could open promising avenue for better therapeutic response. Of note, there is currently no valid biomarker to predict lung cancer sensitivity in patients during treatment. Since genetic variations cause many challenges in treating patients, genotyping of known polymorphisms must be thoroughly explored to find desirable treatment platforms. With this knowledge, individualized treatments could become more possible in management of LC.

1. Introduction

Lung cancer has been reported to have the greatest incidence rate worldwide for many years [1]. In 2020, a total of 2.2 million lung cancer cases were diagnosed worldwide of whom 1.8 million died [2]. The regions with the most significant incidence rates of this cancer are Micronesia/Polynesia, Central and Eastern Europe, and Eastern Asia. Incidence rates in women are typically lower than that of men. With the advancement of screening protocols, lung cancer mortality rates have decreased to 48 % in men and 23 % in women. However, more people are predicted to die from lung cancer in the near future [3].

The supreme risk factor for lung cancer occurrence is tobacco usage [4]. It has been proven that second-hand smoke also increases the risk of developing lung cancer by about 26 % [4]. Other citable risk factors include positive family history and exposure to asbestos or toxic materials such as polycyclic aromatic hydrocarbons, heavy metals, and radon gas [5].

Based on the histological findings, small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) are the two main types of lung cancer [6]. NSCLC, including large cell carcinoma, squamous cell carcinoma, and adenocarcinoma, accounts for approximately 85 % of lung cancer cases. In comparison, 15 % of all lung cancer cases are SCLC [7]. NSCLC has a higher 5-year survival rate (23 %)

than SCLC (6 %) [8].

Nowadays, the best treatment modality for SCLC in limited stages is the simultaneous use of chemotherapy and radiotherapy [9]. The preferred chemotherapy approach includes a platinum-based regimen in combination with etoposide and thoracic radiotherapy once or twice a day before the third cycle of chemotherapy [10]. Treatment scenarios for NSCLC vary depending on the stage of the disease and the patient's condition [11] They generally consist of surgery, radiation therapy, chemotherapy, immunotherapy, and molecularly targeted therapy, which may be chosen alone or together with other forms of treatment [12].

In the past few years, practical advances have been made not only in surgical and radiotherapeutic techniques, but also in knowledge of cancer biology, which significantly enhance care standards of cancer patients in terms of progression-free survival, overall response rates, and patient quality of life [13]. In this context, immunotherapy is expected to fundamentally change the standards of long-term cancer patients' care [14]. As an example, immune checkpoint blockade is an immunotherapy technique that has recently gained popularity in cancer treatment, which can be used alone or in combination with other therapies, such as radiotherapy or chemotherapy [15]. Initial clinical trials have been shown that a successful combination of these therapies improves the success rate of treatment [16]. However, it has remained a challenge to find a successful treatment modality, especially for tumors resistant to radiation and chemotherapy and for patients at high risk of involvement of normal tissues [17]. It is still unclear whether the combination of immunotherapy and radio(chemo)therapy increases the risk of complications in normal tissues, mainly due to the fact that the toxicity induced by chemo and radiotherapy in normal tissues may involve immunologic processes [18]. As a result, clinical trials investigating the combination of radiotherapy and immunotherapy are receiving much attention not only for their efficacy, but also for the project's safety [19].

Recently, treatment paradigm of lung cancer has been shifted to the evolution of targeting a wide ranges of oncogenes to reverse drug resistance and improve the use of personalized medicine with the aim of promoting quality of life and survival of patients. One of the beneficial approaches to design clinical setting and evaluate therapeutic outcomes is evaluating the patient's genetic polymorphism which open a promising avenue towards personalized medicine [20]. Based, this article provides insight into the importance of non-coding RNA polymorphisms in therapeutic response of lung cancer, which allow to find the pharmacogenomics of drug-based toxicities in lung cancer patients and comprehensively assess the association between genetic polymorphisms and drug response in lung cancer patients.

1.1. Role of polymorphisms in cancer therapy

Variations in human phenotype are often caused by genetic and environmental factors [20] Genetic variations, known as polymorphisms, describe the occurrence of different phenotypes in a given population. A variation in the DNA sequence that is not a mutation is called polymorphism [21]. Genetic polymorphisms occur when a gene has two or more equivalent sequences alongside at least 1 % frequency of the common allele in the population [22]. The allele is recognized as a mutation if its frequency is less than 1 %. From the other point of view, the mutation is a deviation from the normal allele in the DNA sequence, resulting in an aberrant variant [23]. There are several types of polymorphisms, depending on the region they affect, such as single nucleotide polymorphisms (SNPs) that vary a single nucleotide, tandem repeat polymorphisms that vary DNA sequences multiple times in their non-coding regions, short tandem repeats that vary DNA sequences by repeating units of one to six base pairs, and copy number polymorphisms that alter large sections of a genome [24]. Genetic polymorphisms as a whole make a broad genetic variety in the population [25].

In an average, the genomes of a human has been found to contain 85 million SNPs [26]. Each SNP provides a consistent point of variance in a patient's drug response [27] Polymorphisms affect pharmacodynamics which refers to how well receptors, ion channels, and other different targets respond to medicines and pharmacokinetics which refers to how drugs move through the body and how drugs are absorbed, distributed, and metabolized [28]. So, the treatment processes can be affected by any of these variables. For example, changes in just one nucleotide of the genes encoding drug transporters, targets, and metabolizing enzymes can alter drug performance in the patient's body [29]. To this notion, Ahmed et al. checked out the effects of drug response in individuals and found that genetic factors are responsible for 20–95 % of the variation in medication response in a population [28]. Some polymorphisms may result in the decrease or loss of function of proteins which are necessary for the drug performance accompanied by serious side effects of some medications [30].

Oncologic therapies have evolved and become better adapted to the different polymorphisms of patients [31]. The proper chemotherapeutic medication for a patient can be chosen if the polymorphisms are understood and identified early in the patient's course of treatment [32]. For instance, there are numerous polymorphisms in the cytochromes P450 (CYPs) enzymes that control drug metabolism. In one hand, the CYP2 enzyme family is particularly vital for the metabolism of anti-cancer drugs [33]. In the other hand, there are lines of evidences shown that the prodrug Tegafur is converted by CYP2A6 enzymes into 5-fluorouracil (5-FU), a potent antitumor agent. Patients carrying the CYP2A6*4 allele have a lower ability to convert Tegafur to 5-FU, which reduced their response to treatment [34]. While, patients carrying the CYP2A6*1B variant have higher conversion rates of Tegafur to 5-FU [34].

Taken together, to select the appropriate drug, it is essential to know whether a patient has particular mutations. In a more detail, genotyping of known polymorphisms must be thoroughly explored and used for treatment options, as genetic variations continue to provide opportunities and challenges for physicians in treating patients [35].

1.2. Non-coding RNA polymorphisms and lung cancer

Depending on the number of nucleotides, non-coding RNAs (ncRNAs) can be divided into short and long ncRNAs (lncRNAs) [36]. Short ncRNAs include small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), ribosomal RNAs (rRNAs), transfer RNAs

(tRNAs), piwi interacting RNAs (piRNAs), and other RNAs with known and unknown functions [37]. LncRNAs are a subclass of RNA molecules that are less conserved than miRNAs and are usually longer than 200 nt [38]. It has been confirmed that the dysregulation of lncRNAs in a transcriptional levels has a pivotal impact on metastasis, proliferation, and drug resistance in lung cancer.Also, miRNAs could directly or indirectly affect the expression of genes involved in drug transportation, drug targets, drug metabolism, and downstream signal molecules. Because ncRNAs polymorphisms could serve as biomarkers to predict cancer patients' response to therapy, in this review, we explained a number of non-coding gene polymorphisms affecting response to LC cancer therapies. With this knowledge, individualized oncology treatments might be more thinkable.

1.3. The mechanism of non-coding RNAs and resistance to therapies

Emerging evidence indicates that dysregulation of miRNAs, lncRNAs, and circular RNAs could modulate the expression of target genes involved in autophagy, cellular apoptosis, drug efflux, and cancer stem cells (CSCs), and epithelial-to-mesenchymal transition (EMT), resulted in promotion of cancer drug resistance. Commonly, the mechanism by which miRNAs could regulate resistance to cancer therapies is mediated by targeting apoptotic pathways and the activity of drug efflux pumps.

Furthermore, ncRNAs have a substantial role in genomic stability and mutagenesis via involvement in DNA repair machinery. In this regard, studies showed that ncRNAs could affect DNA damage response (DDR) signaling pathways. Molecularly, DNA damage affect the ncRNAs (particularly, miRNAs and lncRNAs) expression which in turn could alter the expression of interest genes involved in DDR followed by various response to drugs. Therefore, finding the potential ncRNAs interacting with any of the above-mentioned pathways could be promising approach to overcome the LC conventional therapies.

1.4. LncRNA and resistance to lung cancer therapies

Previous research has shown that lncRNAs have critical functions by interacting with chromatin-associated proteins and playing vital roles in chromatin remodeling, transcription, and post-transcriptional processing [39,40]. LncRNAs affect gene expression via cis or trans action manner [41] For example, a small number of lncRNAs, such as the X Inactive Specific Transcript (XIST), control genomic imprinting in cis mode [42]. Numerous biological processes, such as gene expression, cell differentiation, organogenesis, and homeostasis, depend on the basal expression of lncRNAs in human tissues. An increasing number of studies have suggested that the dysregulation of these lncRNAs in the human genome plays a role in developing hematologic or solid malignancies. These include XIST [43], HOX antisense intergenic RNA (HOTAIR) [44], and Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1) [45]. Only 19 % of protein-coding genes show differential expression patterns, whereas 78 % of human lncRNAs are more tissue-specific [46]. Consequently, functional classification of tumor-associated lncRNAs (including oncogenes or tumor suppressors) could lead to developing unique cancer biomarkers [47].

In the last decade, many lncRNAs have been discovered to be abnormally expressed in lung cancer [48]. In addition, lncRNAs have received increasing attention as biomarkers for initial cancer diagnosis, prognosis, and treatment response assessment [48–50]. Differential tumor prognosis is associated with dysregulation of lncRNAs in specific histologic subtypes of lung cancer [51]. For instance, in contrast to lung adenocarcinomas (LUADs), SRY-Box Transcription Factor 2 (SOX2)-overlapping transcript (SOX2-OT) has been

Table 1

The association between lncRNAs or their polymorphisms and resistance to lung cancer therapies.

LncRNAs	Therapeutic resistance	Mechanism	Outcome	Ref
SOX2-OT	tyrosine kinase inhibitor (TKI)-erlotinib and cisplatin	Regulation of AKT/ERK and SOX2/GLI-1 expression	promoting poor prognosis and human lung malignancy	(59)
MALAT1	Docetaxel	sponging miR-200b to upregulate E2F3 and ZEB1	Modulation of the chemoresistance in DTX-resistant lung adenocarcinoma cells	(60)
HOTTIP	SCLC chemoresistant cell lines	binding to miR-216a and reversing its anti-tumor activity alongside elevated expression of BCL-2	SCLC progression and chemoresistance	(61)
Linc00173	SCLC chemoresistant cell lines	sponging miR-218 to regulate Etk expression	increasing SCLC cell chemoresistance, proliferation, and invasion alongside advanced stage and shorter survival of SCLC cases	(62)
CASC8 rs10505477 Polymorphism	Platinum-based chemotherapy	still unclear	affecting risk of lung cancer, outcome of platinum-based chemotherapy, severe hematologic toxicity in the NSCLC subgroup, and gastrointestinal toxicity in SCLC and cisplatin subtypes	(64)
-ANRIL rs1333049 -MEG3 rs116907618	platinum-based chemotherapy regimen	-ANRIL controls the epigenetic silencing of p16INK4a and p14ARF, which regulate apoptosis induced by cisplatin -rs116907618 might change folding and function of MEG3	-severe gastrointestinal toxicity and overall toxicity -severe gastrointestinal toxicity	www.ncbi.nlm.nih.gov/pmc/articles/PMC5386317/ [57]

typically observed in squamous cell carcinomas (SCCs) of the lung [52]. In patients with LUADs, poor survival is related to the high expression of SOX2-OT, whereas outcomes improve in patients with SCCs [53]. Nevertheless, there has been conflicting evidence on the function of SOX2, suggestive of needing further in-depth researches [54].

In this section, we summarize different studies regarding the role of lncRNAs or their polymorphisms on therapeutic responses to further clarify the potential of them as predictive biomarkers in LC.

Chemoresistance continues to be a significant barrier to effective treatment. Numerous lncRNAs have been associated with resistance to chemo-based therapies in lung cancers (Table 1), including cisplatin (CDDP)-based treatment (Fig. 1) [55]. For example, the lncRNA SOX2-OT has been shown to contribute to not only CDDP and tyrosine kinase inhibitor (TKI)-erlotinib resistance, but also poor clinical outcomes in lung cancer patients. AKT signaling activity and increased expression of SOX2 and GLI-1 may contribute to this. In addition, the inhibition of SOX2-OT and reduced expression of SOX2/GLI-1 make lung cancer cells more susceptible to EGFR/TKI-erlotinib or cisplatin [56].

Chen et al. investigated the potentials lncRNAs associated with downregulation of miR-200b in DTX-resistant LUAD and found that MALAT1 could regulate the expression of miR-200b. Mechanistically, MALAT1 controlled miR-200b expression via competing endogenous RNA (ceRNA) pathway. Also, the MALAT1 activity in DTX-resistant LUAD cells could be modulated by miR-200b targets, E2F transcription factor 3 (E2F3) and zinc-finger E-box binding homeobox 1 (ZEB1). Besides, ZEB1 and Transcription factor AP-2 gamma (TFAP2C) could activate MALAT1 followed by sponging miR-200b and resistance of LUAD cells to DTX-based therapy [58].

According to Sun et al. study [59], HOTTIP, a lncRNA frequently elevated in SCLC, is linked to SCLC cell proliferation, chemo-sensitivity, and a bad prognosis. In addition, mechanistic studies have demonstrated that HOTTIP acts as an oncogene in the development of SCLC by binding to miR-216a and reversing its tumor suppressive role in this situation. Moreover, other findings showed that HOTTIP elevated the expression of BCL-2, an essential miR-216a target gene that inhibits apoptosis, which increased the chemoresistance of SCLC to chemotherapy. Their results showed that HOTTIP is involved in developing SCLC and chemoresistance, indicating its potential as a novel diagnostic and prognostic biomarker for SCLC clinical measures.

According to Zeng et al. study [60], high expression of long intergenic non-protein coding RNA 173 (Linc00173) increased SCLC cell chemoresistance, proliferation, and invasion alongside advanced stage and shorter survival of SCLC cases. Similarly, animal studies confirmed that Linc00173 caused SCLC cell proliferation and the development of chemoresistance in tumors. Mechanistically, Linc00173 could upregulate Etk mediated via miRNA-218 sponging and increased expression of GSKIP and NDRG1 followed by translocation of β-catenin. Overall, the mechanism by which Linc00173 promotes chemoresistance and progression of SCLC, suggestive of a potential therapeutic approach against SCLC.

The lncRNA *CASC8* rs10505477 polymorphism has been associated with the risk of several cancers, including colorectal, gastric and invasive ovarian cancers [61]. The association between the *CASC8* rs10505477 polymorphism and lung cancer risk was investigated in a Chinese population by genotyping 498 lung cancer patients and 213 healthy controls [62]. Four hundred sixty-seven out of the 498 patients were chosen for the studying the correlation between this polymorphism with toxicity and response to treatment. In a recessive model, they discovered that the SNP rs10505477 has a strong correlation with the risk of lung cancer in male and adenocarcinoma subgroups. In the dominant model, there was a similarly strong association with the outcome of platinum-based chemotherapy. Furthermore, it was found that both the dominant model and the additive model showed a strong link between the *CASC8* rs10505477 polymorphism and severe hematologic toxicity in the NSCLC subgroup. Also, it was discovered that in the dominant model, the rs10505477 polymorphism was strongly linked to gastrointestinal toxicity in SCLC and cisplatin subtypes [62]. Consequently, lncRNA *CASC8* rs10505477 can be used as a risk factor for lung cancer diagnosis and as a predictor of the efficacy and adverse effects of platinum-based therapy.

In another research, Gong et al. investigated the association between lncRNA polymorphisms and gastrointestinal and hematological toxicities of platinum-based chemotherapy in Chinese lung cancer patients (n = 467). Then, functional polymorphisms were
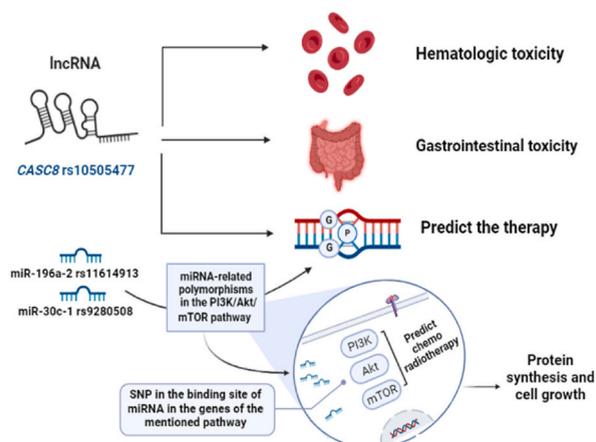

Fig. 1. Representation of lncRNAs, reported in bold, involved in cisplatin resistance in LC Cancer Therapy (Created by Biorender.com).

genotyped within 8 lncRNAs (ANRIL, CCAT2, HOTTIP, H19, HOTAIT, MEG3, MALAT1, and POLR2E). The results demonstrated that ANRIL rs1333049 was associated with severe gastrointestinal toxicity and overall toxicity. Also, MEG3 rs116907618 was linked with severe gastrointestinal toxicity. The best model to predict hematological toxicity was POLR2E rs3787016-HOTTIP rs3807598-chemotherapy regimen. Therefore, genetic polymorphisms in ANRIL and MEG3 are associated with severe toxicity of platinum and could be used to evaluate pretreatment in Chinese lung cancer patients.

Collectively, the results of this section present evidence that lncRNAs or their polymorphisms could be associated with orchestrated resistance mechanisms in lung cancers through genetic, epigenetic, and post-translational modifications, which could emphasize their role as a therapeutic predictor in different-chemo-based therapies.

1.5. MiRNA and resistance to lung cancer therapies

A small group of non-coding RNAs that are transcribed by RNA polymerase II is called microRNAs [63]. These nucleic acids are essential regulators of gene expression and normally prevent mRNA translation [64]. Several blood-based miRNA assays have been created to diagnose lung cancer with adequate sensitivity and specificity, which is the result of recent intensive research on disease-regulated miRNAs [65]. In addition, miRNAs that predict response to treatment are provided [50,66]. The main barrier limiting the curative efficacy of traditional anti-cancer therapies is treatment resistance [67]. Recent research has demonstrated that miRNAs are involved in developing resistance by controlling the expression of genes linked with resistance (Table 2) [68]. However, the fundamental cause of medication resistance in lung cancer is not entirely known [69].

Costantini et al. reported that overexpression of miR-320b and miR-375 has been linked with resistance to Nivolumab therapy. According to the results of bioinformatics databases, it was found that miRNA-320b could noticeably attach to the proliferation genes (*MYC, TUBB1*) and miRNA-375 could notably target tumor migration (*NCAM1, CDH2*), immune-related (*JAK2, TGF-β2*), proliferation (*MYC*), Wnt pathway (*FZD4, FZD8*), and Hippo pathway (*YAP1*) genes [70]. Also, increased levels of circulating miR-93, 138-5p, 200, 27a, 424, 34a, 28, 106b, 193a-3p, and 181a predicted response to Nivolumab therapy (anti-PD1 drug), especially with a significant improvement in progression-free survival (PFS) and overall survival (OS) of patients. These results demonstrated that alterations in circulating miRNAs are associated with the response and outcome in NSCLC patients treated with anti-PD1 drugs. The main biological pathways by which the above-mentioned miRNA signatures could regulate response to anti-PD1-therpy could be defined as follows; fatty acid biosynthesis, proteoglycans in cancer, TGF-beta signaling pathway, pathways in cancer, Wnt signaling pathway, and Ras

Table 2
The association between miRNAs and resistance to lung cancer therapies.

miRNAs	Therapeutic resistance	Mechanism	Outcome	Ref
miR-320b and miR-375	Nivolumab therapy	miRNA-320b could noticeably attach to proliferation genes and miRNA-375 could notably target tumor migration, immune-related, proliferation, Wnt pathway, and Hippo pathway genes	overexpression of miR-320b and miR-375 has been linked with resistance to Nivolumab therapy	(71)
miR-93, 138-5p, 200, 27a, 424, 34a, 28, 106b, 193a-3p, and 181a	Nivolumab therapy (anti-PD1-therpy)	Through biological pathways, such as fatty acid biosynthesis, proteoglycans in cancer, TGF-beta signaling pathway, pathways in cancer, Wnt signaling pathway, and Ras signaling pathway.	Prediction of the response to checkpoint inhibitor anti-PD-1 therapy in non-SCLC and significant improvement in progression-free survival (PFS) and overall survival (OS) of patients	(72)
miR-181c	Cisplatin	Targeting Wnt inhibitory factor (WIF1)	Affecting survival rate and CDDP-induced apoptosis	(73)
miR-7	Cellular model of a human SCLC-drug resistant cell line (H69AR)	Suppression of MRP1/ABCC1	Overall survival rate and drug response in SCLC patients correlated significantly with low levels of miR-7 expression	(74)
miR-21	EGFR-TKI inhibitor	Down-regulating PTEN and PDCD4 and activating PI3K/Akt pathway	Involved in acquired resistance of EGFR-TKI in NSCLC	(75)
miR-21	Carboplatin	Inhibition of SMAD7, a critical inhibitor of TGF receptor activation	Regulation of responsiveness of NSCLC cells to carboplatin	(76)
miR-21	Radioresistance in NSCLC	Increasing HIF1-induced glycolysis	Associated with oncogenesis and radioresistant in NSCLC	(77)
miRNA 221/222, miRNA 30b-c, miR-103 and miR-203	Gefitinib tyrosine kinase inhibitors (TKIs),	Blockade of the expression of the genes encoding apoptotic peptidase activating factor 1 (APAF-1), protein kinase C ϵ (PKC-ϵ), BCL2-like 11 (BIM), and sarcoma viral oncogene homolog (SRC)	Prediction of successful treatments	(78)
miR-134/487b/655 cluster	Gefitinib	Targeting MAGI2	Contributing to the TGF-1-induced EMT phenomena	(79)
miR-208a	Resistance to radiation	Targeting p21 in lung cancer cells and activating the AKT/mTOR pathway	Affecting the proliferation and radiosensitivity of human lung cancer cells	(83)
miR-25	Ionizing radiation (IR)	Direct targeting of BTG2 in NSCLC cancer	Affecting sensitivity to the radiotherapy	(84)
microRNA-1323	Radioresistance in NSCLC	Targeting DNA-activated, catalytic polypeptide (PRKDC) which affctes DNA repair	Regulation of sensitivity of cancer cells to radiation	(85)

signaling pathway [71].

Zhang et al. demonstrated that miR-181c could targets Wnt inhibitory factor (WIF1) leading to CDDP resistance in NSCLC cells Therefore, XAV939 treatment of CDDP-resistant NSCLC could improve sensitivity of current cells to CDDP, which could in a favor of promoting survival rate and CDDP-induced apoptosis [72].

Similarly, Liu et al. [73] investigated the functional role of miR-7 in the mechanisms underlying the chemoresistance of SCLC to chemotherapy. They understood that MRP1/ABCC1 is a possible target gene of miR-7 evidenced by bioinformatics analysis. Also, 44 SCLC samples were analyzed by qRT-PCR and immunohistochemistry to investigate the expression of miR-7 and MRP1/ABCC1. The results revealed that OS rate and drug response in SCLC patients were significantly correlated with low levels of miR-7 expression but not with sex, age, or stage. There was an inverse correlation between expression of MRP1/ABCC1 and miR-7. To address this, transfection of H69 AR cells with a miR-7 mimic downregulated MRP1/ABCC1 levels. Besides, transfection of H69 cells with miR-7 inhibitor recovered MRP1/ABCC1 expression. Since miR-7 specifically targeted expected sites in the 3′-UTR of the MRP1/ABCC1 gene, as shown by a dual-luciferase reporter test, miR-7 could be a prognostic indicator and possible therapeutic target in human SCLC as it mediates SCLC chemoresistance via suppression of MRP1/ABCC1. In another study, Li et al. [74] showed that miR-21 affects epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) acquired resistance in NSCLC by downregulating PTEN and PDCD4 and activating the PI3K/Akt pathway. In this regard, it was demonstrated that EGFR-TKI resistant cell line (PC9R) could overexpress miR-21 compared to EGFR-TKI-sensitive human lung adenocarcinoma cell line (PC9). Also, the miR-21 expression in serum of NSCLC patients received EGFR-TKI was notably higher at the acquiring resistance time than baseline. While knockdown of miR-21 in PC9R cell line induced apoptosis in mice model treated with EGFR-TKI. Others indicated that miR-21 inhibits SMAD7, a critical inhibitor of TGF receptor activation, and reduces the responsiveness of NSCLC cells to carboplatin [75]. By increasing hypoxia-inducible factor-1α (HIF1α)-induced glycolysis, miR-21 promotes radioresistance in NSCLC. So, cancer cells could be resensitized to the radiation therapy by suppression of HIF1α [76].

Garofalo et al. showed the direct link between EGF and EMT with oncogenic miRNAs, such as miRNA 221/222 and miRNA 30b/c. They reported that miR-221/222 and miR-30b/c modulated by both EGF and MET receptors, whereas miR-103 and miR-203 could only be mediated by MET. These miRs could affect gefitinib-induced apoptosis and EMT of NSCLC cells via blocking the expression of the genes encoding apoptotic peptidase activating factor 1 (APAF-1), protein kinase C ε (PKC-ε), BCL2-like 11 (BIM), and sarcoma viral oncogene homolog (SRC). Therefore, downregulating these miRNA genes may represent a potential avenue for more successful treatments [77]. The study of Kitamura et al. on gefitinib resistance demonstrated that the miR-134/487b/655 cluster directly targets MAGI2, which its decrease causes the loss of PTEN stability in NSCLC cells and contributes to the TGF-1-induced EMT phenomena [78].

Evidence has shown that microRNAs can regulate cellular responses to radiation in several ways [79–81]. In a study using miRNA microarray technology, Tang et al. [82] discovered that miRNAs in serum of lung cancer patients have a different expression profile before and after radiation therapy. They further investigated the possible mechanism by studying the biological effects of miR-208a on cell survival, apoptosis, and cell cycle distribution in human lung cancer cells. They showed that only miR-208a was up-regulated in patients' blood after radiotherapy, while nine miRNAs, including miR-29b-3p, miR-200a-3p, and miR-126-3p, were considerably down-regulated. Also, X-rays can stimulate miR-208a expression in lung cancer cells. Moreover, targeting p21 in lung cancer cells by increasing the expression of miR-208a and activating the AKT/mTOR pathway leads to enhanced cell growth and resistance to radiation. In contrast, the downregulation of miR-208a has the opposite effect. Moreover, downregulation of miR-208a in NSCLC cells prevented G1 phase arrest and increased the proportion of cells undergoing apoptosis. Furthermore, time-dependent transport of miR-208a, derived from lung cancer patients' serum exosome fraction, to a549 cells could probably involve in the subsequent biological consequences. This research has shown that miR-208a, targeting the p21 gene and delivered by exosomes, can impact the radiosensitivity and proliferation of human lung cancer cells. As a result, miR-208a could be a possible therapeutic target for people with lung cancer [82].

In the radioresistant NSCLC, miR-25 could be upregulated followed by decreased radiation sensitivity via binding to B-cell translocation gene 2 (BTG2) [83]. Li et al. showed that the expression of miR-1323 could increase by > 5-fold in the radioresistant NSCLC cells via targeting DNA-activated, catalytic polypeptide (PRKDC) which affects DNA repair. In a way that miR-1323 inhibition enhanced the sensitivity of cancer cells to radiation [84].

1.6. MiRNA polymorphisms and lung cancer therapies

MiRNA polymorphisms (miRSNPs) can be found in genes associated with miRNA biogenesis, miRNA binding sites of target genes, and mature, pri-, and pre-miRNA sequences. Various miRSNPs are involved in survival or chemotherapy toxicity of LC. Zhan et al. screened the *miR-196a2* rs11614913 polymorphism in 442 Chinese patients with NSCLC after platinum-based regimen. The result showed that *miR-196a2* rs11614913 C > T polymorphism could change expression and function of mature miRNA. Also, rs11614913 CC homozygotes demonstrated higher occurrence of OS especially in cases treated with gemcitabine or cisplatin as well as younger and male patients Xu et al. genotyped rs895819 in *pre-miR-27a in* 576 NSCLC patients and found that the G allele of this polymorphism was linked with reduced response to platinum-based chemotherapy, indicative of the influence of *pre-miR-27a* rs895819 polymorphism on clinical outcome of NSCLC patients

Fang et al. [85] found that miRNA expression can be affected by SNPs in miRNA involved in miRNA synthesis and structural modification. They aim to determine whether functional miRNA variations are related to lung cancer susceptibility and response to platinum-based treatment. In this regard, MALDI-TOF mass spectrometry was used to genotype nine genetic SNPs in miR-605, 146a, 149, 196a-2, 27a, 499, 30c-1, 5197, and let 7a-2 in a total of 215 healthy controls and 507 lung cancer patients (at least two

consecutive cycles of platinum-based chemotherapy were administered to 386 patients). The results of their work are shown in Table 3.

These results indicated that polymorphisms of miR-30c-1 (rs9280508) and miR-196a-2 (rs11614913) have a significant impact on how well patients respond to platinum-based chemotherapy. In addition, an association was found between the prevalence of lung cancer and the SNPs rs71428439 (miR-149), rs2910164 (miR-146a), rs928508 (mir-30c-1), and rs629367 (let-7a-2). These SNPs could be used as possible clinical biomarkers to assess lung cancer risk and the efficacy of platinum-based chemotherapy [85].

The PI3K/Akt pathway is essential for the growth and management of cancer, particularly SCLC, which has a notoriously poor prognosis [86]. Regarding to this reason, Jiang et al. [87] investigated the relationship between SNPs at the 3′UTR of genes (the binding site of miRNAs) in the mTOR pathway and the prognosis of patients with limited disease SCLC. One hundred forty-six patients with the limited disease SCLC who received chemoradiotherapy (etoposide + cisplatin or etoposide + carboplatin) were the subject of this retrospective study. The genotypes of nine SNPs in six genes of the mTOR pathway were determined from blood samples. Three SNPs, including MTOR: rs2536 (T > C), PIK3R1: rs3756668 (A > G), and PIK3R1: rs12755 (A > C) were linked to increased overall survival. This study found that miRNA SNPs associated with the PI3K/Akt/mTOR pathway could be useful biomarkers to supplement clinicopathological factors in predicting the prognosis of limited disease SCLC and help select patients who would benefit from chemoradiotherapy [87].

Although there is published evidence about the association between miRNAs and therapy in LC, the correlation between miRNAs polymorphism and drug resistance, which could serve as an effective targeted therapy in LC, has not been fully elucidated.

2. Future perspective

The location and stage of the tumor as well as the patient's general health help to choose the cancer chemotherapeutic drugs and their dosage [88]. Pharmacogenetics has enabled personalized treatments for chemotherapy, radiation, and targeted therapies based on the patient's genetic information [89]. For physicians, genetic data from polymorphism-based pharmacogenetic studies are essential for better prediction of drug response and potentially fatal side effects. Pharmacogenotyping has employed various screening techniques, including SNP analysis, somatic and germline mutation analysis, and partial and whole genome sequencing [23]. With the accumulation of data revealing human genomic variation from large-scale populations and multi-parameter-based pharmacogenetic studies in the post-genomic era, the promising impact of pharmacogenetics on resolving individual variability in medication response and toxic responses is being observed [90]. Large variations in the human genome are caused by polymorphisms, which can also affect the pharmacokinetics and pharmacodynamics of pharmaceuticals and the cellular response to therapeutic approaches. Predicting altered pharmacokinetics of therapeutics requires determining the effects of polymorphisms on chemotherapeutic drug targets. It is critical to explain significant gene polymorphisms and their clinical significance in cancer, as they may influence the best optimum pharmaceutical treatment in terms of efficacy, tolerability, and adverse effects [91].

The response of LCpatients to radiotherapy or chemotherapy could be related to polymorphisms in non-coding RNAs, which supports the idea that genetic variations affecting DNA repair or apoptosis pathways may influence the response to therapies. Of note, copy number variations (CNVs) in miRNA genes (CNV-miRNAs) also could affect miRNA binding and regulation of its target genes. It should be mentioned that CNV refer to the genomic DNA segments with different copy numbers in the genome because of deletions or duplications. So, identification of polymorphic CNV regions could be implied into pharmacogenomics and personalized medicine. Ethnic difference in drug response is another important point which could be defined by different frequencies of miRNAs polymorphisms in various population. Since the evidence supporting the aforementioned associations have not been comprehensively elucidated, further studies are needed to reinforce the clinical importance of non-coding RNAs polymorphisms as future predictive biomarkers in LCmanagement. All of which help to prevent the drug resistance and its undesirable side effects during LC treatments.

Ethics approval and consent to participate

Not applicable.

Authors Contributions

Data availability statement: In this review study, the data available in the reliable scientific databases available on the Internet, which are available to the public, have been used.

Table 3
The association between genetic SNP in miRNAs and lung cancer risk as well as response to platinum-based chemotherapy.

Trait	P value	Allele	Polymorphisms	Gene
high risk of lung cancer	0.022	C/G	rs2910164	miR-146a
high risk of lung cancer	0.042	C	rs71428439	miR-149
high risk of lung cancer in age under 57 years	0.030	–	rs629367	Let-7a-2
high risk of lung cancer in age under 57 years	0.005	–	rs928508	miR-30c-1
sensitive to platinum	0.010	C	rs11614913	miR-196a-2
sensitive to platinum	0.022	G	rs9280508	miR-30c-1

CRediT authorship contribution statement

Samaneh Mollazadeh: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Negar Abdolahzadeh:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Meysam Moghbeli:** Conceptualization, Writing – original draft, Writing – review & editing. **Fatemeh Arab:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Ehsan Saburi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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.

References

[1] F. Bray, et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA: a cancer journal for clinicians 68 (6) (2018) 394–424.

[2] https://gco.iarc.fr/today/fact-sheets-cancers.

[3] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, CA Cancer J Clin, 2020 70 (1) (2020) 7–30.

[4] M.O.K. Linda, et al., Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis, BMJ Open 8 (10) (2018), e021611.

[5] F. Minichilli, et al., Risk factors for lung cancer in the Province of Lecce: results from the PROTOS Case–control study in Salento (Southern Italy), Int. J. Environ. Res. Publ. Health 19 (14) (2022) 8775.

[6] A. Ullah, et al., Clinicopathological and treatment patterns of combined small-cell lung carcinoma with future insight to treatment: a population-based study, J. Clin. Med. 12 (2023), https://doi.org/10.3390/jcm12030991.

[7] https://www.ncbi.nlm.nih.gov/books/NBK482458/.

[8] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, CA Cancer J Clin, 2019 69 (1) (2019) 7–34.

[9] D. Almquist, K. Mosalpuria, A.K. Ganti, Multimodality therapy for limited-stage small-cell lung cancer, Journal of oncology practice 12 (2) (2016) 111–117.

[10] Y. Wang, et al., New insights into small-cell lung cancer development and therapy, Cell Biol. Int. 44 (8) (2020) 1564–1576.

[11] S. McMullen, et al., Treatment decisions for advanced non-squamous non-small cell lung cancer: patient and physician perspectives on maintenance therapy, The Patient-Patient-Centered Outcomes Research 12 (2019) 223–233.

[12] Z. Abbas, S. Rehman, An overview of cancer treatment modalities, Neoplasm 1 (2018) 139–157.

[13] L.W. Elmore, et al., Blueprint for cancer research: critical gaps and opportunities, CA A Cancer J. Clin. 71 (2) (2021) 107–139.

[14] K. Esfahani, et al., A review of cancer immunotherapy: from the past, to the present, to the future, Curr. Oncol. 27 (s2) (2020) 87–97.

[15] S. Yu, et al., Effective combinations of immunotherapy and radiotherapy for cancer treatment, Front. Oncol. 12 (2022) 231.

[16] R. Bayat Mokhtari, et al., Combination therapy in combating cancer, Oncotarget 8 (23) (2017) 38022–38043.

[17] K. Wang, J.E. Tepper, Radiation therapy-associated toxicity: Etiology, management, and prevention, CA A Cancer J. Clin. 71 (5) (2021) 437–454.

[18] F. Wirsdörfer, S. De Leve, V. Jendrossek, Combining radiotherapy and immunotherapy in lung cancer: can we expect limitations due to altered normal tissue toxicity? Int. J. Mol. Sci. 20 (1) (2018) 24.

[19] L. Meng, et al., The combination of radiotherapy with immunotherapy and potential predictive biomarkers for treatment of non-small cell lung cancer patients, Front. Immunol. 12 (2021), 723609.

[20] A.C. Gummadi, A.K. Guddati, Genetic polymorphisms in pharmaceuticals and chemotherapy, World J. Oncol. 12 (5) (2021) 149.

[21] R. Karki, et al., Defining "mutation" and "polymorphism" in the era of personal genomics, BMC Med. Genom. 8 (2015) 1–7.

[22] S.S. Aga, M.Z. Banday, S. Nissar, Genetic Polymorphism and Disease, CRC Press, 2022.

[23] G.C. Kocal, Y. Baskin, Polymorphisms in pharmacogenetics of personalized cancer therapy, Genetic Polymorphisms 1 (2017).

[24] F. Robert, J. Pelletier, Exploring the impact of single-nucleotide polymorphisms on translation, Front. Genet. 9 (2018) 507.

[25] M. Milad, et al., Polymorphic SNPs, Short Tandem Repeats and Structural Variants Are Responsible for Differential Gene Expression across C57BL/6 and C57BL/10 Substrains, bioRxiv, 2021, p. 2020, 03.16.993683.

[26] J. van Arensbergen, et al., High-throughput identification of human SNPs affecting regulatory element activity, Nat. Genet. 51 (7) (2019) 1160–1169.

[27] J.v. Arensbergen, et al., Systematic Identification of Human SNPs Affecting Regulatory Element Activity, bioRxiv, 2018, 460402.

[28] B. Franczyk, J. Rysz, A. Gluba-brzózka pharmacogenetics of drugs used in the treatment of cancers, Genes 13 (2022), https://doi.org/10.3390/genes13020311.

[29] S. Ahmed, et al., Pharmacogenomics of drug metabolizing enzymes and transporters: relevance to precision medicine, Dev. Reprod. Biol. 14 (5) (2016) 298–313.

[30] V.M. Lauschke, L. Milani, M. Ingelman-Sundberg, Pharmacogenomic biomarkers for improved drug therapy—recent progress and future developments, AAPS J. 20 (1) (2017) 4.

[31] T. Zhao, 243P the effects of genomic polymorphisms in one-carbon metabolism pathways on survival of gastric cancer patients received fluorouracil-based adjuvant therapy, Ann. Oncol. 27 (2016) ix76.

[32] L.A. Colvin, Chemotherapy-induced peripheral neuropathy (CIPN): where are we now? Pain 160 (Suppl 1) (2019) S1.

[33] S. Pathania, et al., Drug metabolizing enzymes and their inhibitors' role in cancer resistance, Biomed. Pharmacother. 105 (2018) 53–65.

[34] H. Wang, et al., Association analysis of CYP2A6 genotypes and haplotypes with 5-fluorouracil formation from tegafur in human liver microsomes, Pharmacogenomics 12 (4) (2011) 481–492.

[35] D. Bertholee, J.G. Maring, A.B. van Kuilenburg, Genotypes affecting the pharmacokinetics of anticancer drugs, Clin. Pharmacokinet. 56 (4) (2017) 317–337.

[36] J. Cao, et al., Non-coding RNA in thyroid cancer-Functions and mechanisms, Cancer Lett. 496 (2021) 117–126.

[37] L.-T. Gou, Q. Zhu, M.-F. Liu, Small RNAs: an Expanding World with Therapeutic Promises, Fundamental Research, 2023.

[38] F.J. Slack, A.M. Chinnaiyan, The role of non-coding RNAs in oncology, Cell 179 (5) (2019) 1033–1055.

[39] K.C. Wang, et al., A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression, Nature 472 (7341) (2011) 120–124.

[40] J.M. Engreitz, N. Ollikainen, M. Guttman, Long non-coding RNAs: spatial amplifiers that control nuclear structure and gene expression, Nat. Rev. Mol. Cell Biol. 17 (12) (2016) 756–770.

[41] N. Gao, et al., Long non-coding RNAs: the regulatory mechanisms, research strategies, and future directions in cancers, Front. Oncol. 10 (2020), 598817.

[42] J. Beermann, et al., Non-coding RNAs in development and disease: Background, mechanisms, and therapeutic approaches, Physiol. Rev. 96 (4) (2016) 1297–1325.

[43] J. Zhao, et al., Polycomb proteins targeted by a short repeat RNA to the mouse X chromosome, Science 322 (5902) (2008) 750–756.

[44] C. Jiang, et al., Long non-coding RNAs: potential new biomarkers for predicting tumor invasion and metastasis, Mol. Cancer 15 (1) (2016) 62.

[45] P. Ji, et al., MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer, Oncogene 22 (39) (2003) 8031–8041.

[46] M.N. Cabili, et al., Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses, Genes Dev. 25 (18) (2011) 1915–1927.

[47] A. Necsulea, et al., The evolution of lncRNA repertoires and expression patterns in tetrapods, Nature 505 (7485) (2014) 635–640.

[48] R. Ye, et al., New insights into long non-coding RNAs in non-small cell lung cancer, Biomed. Pharmacother. 131 (2020), 110775.

[49] A.S. Zangouei, et al., Cell cycle related long non-coding RNAs as the critical regulators of breast cancer progression and metastasis, Biol. Res. 56 (1) (2023) 1.

[50] I. Akhlaghipour, et al., MicroRNA-377: a therapeutic and diagnostic tumor marker, Int. J. Biol. Macromol. 226 (2023) 1226–1235.

[51] J. Jiang, et al., The Emerging roles of long noncoding RNAs as Hallmarks of lung cancer, Front. Oncol. 11 (2021), 761582.

[52] T. Hussenet, et al., SOX2 is an oncogene activated by recurrent 3q26.3 amplifications in human lung squamous cell carcinomas, PLoS One 5 (1) (2010) e8960.

[53] L.M. Sholl, et al., Sox2 protein expression is an independent poor prognostic indicator in stage I lung adenocarcinoma, Am. J. Surg. Pathol. 34 (8) (2010) 1193–1198.

[54] J. Ying, et al., Expression and significance of SOX2 in non-small cell lung carcinoma, Oncol. Lett. 12 (5) (2016) 3195–3198.

[55] X.-Y. Liu, et al., The role of circular RNAs in the drug resistance of cancers, Front. Oncol. 11 (2022), 790589.

[56] A.M. Herrera-Solorio, et al., LncRNA SOX2-OT regulates AKT/ERK and SOX2/GLI-1 expression, hinders therapy, and worsens clinical prognosis in malignant lung diseases, Mol. Oncol. 15 (4) (2021) 1110–1129.

[57] WJ Gong, JB Peng, JY Yin, XP Li, W Zheng, L Xiao, LM Tan, D Xiao, YX Chen, X Li, HH Zhou, ZQ Liu, Association between well-characterized lung cancer lncRNA polymorphisms and platinum-based chemotherapy toxicity in Chinese patients with lung cancer, Acta Pharmacol Sin 38 (4) (2017 Apr) 581–590.

[58] D. Huang, et al., NKILA lncRNA promotes tumor immune evasion by sensitizing T cells to activation-induced cell death, Nat. Immunol. 19 (10) (2018) 1112–1125.

[59] Y. Sun, et al., Long non-coding RNA HOTTIP promotes BCL-2 expression and induces chemoresistance in small cell lung cancer by sponging miR-216a, Cell Death Dis. 9 (2) (2018) 85.

[60] F. Zeng, et al., Linc00173 promotes chemoresistance and progression of small cell lung cancer by sponging miR-218 to regulate Etk expression, Oncogene 39 (2) (2020) 293–307.

[61] Z. Zhang, et al., Role of long non-coding RNA polymorphisms in cancer chemotherapeutic response, J. Personalized Med. 11 (2021), https://doi.org/10.3390/jpm11060513.

[62] L. Hu, et al., Clinical significance of long non-coding RNA CASC8 rs10505477 polymorphism in lung cancer susceptibility, platinum-based chemotherapy response, and toxicity, Int. J. Environ. Res. Publ. Health 13 (6) (2016) 545.

[63] N. Dorraki, et al., miRNA-148b and its role in various cancers, Epigenomics 13 (24) (2021) 1939–1960.

[64] A. Shapouri-Moghaddam, et al., Cardioprotective microRNAs: Lessons from stem cell-derived exosomal microRNAs to treat cardiovascular disease, Atherosclerosis 285 (2019) 1–9.

[65] S. Zhong, et al., miRNAs in lung cancer. A systematic review identifies predictive and prognostic miRNA candidates for precision medicine in lung cancer, Transl. Res. 230 (2021) 164–196.

[66] M.Y. Pratama, et al., Circulatory miRNA as a biomarker for therapy response and disease-free survival in Hepatocellular carcinoma, Cancers 12 (10) (2020).

[67] K. Bukowski, M. Kciuk, R. Kontek, Mechanisms of multidrug resistance in cancer chemotherapy, Int. J. Mol. Sci. 21 (9) (2020) 3233.

[68] X. Ma, A.L. Liang, Y.J. Liu, Research progress on the relationship between lung cancer drug-resistance and microRNAs, J. Cancer 10 (27) (2019) 6865–6875.

[69] G. Li, et al., MiRNA-based therapeutic Strategy in lung cancer, Curr Pharm Des 23 (39) (2018) 6011–6018.

[70] A. Costantini, et al., Predictive role of plasmatic biomarkers in advanced non-small cell lung cancer treated by nivolumab, OncoImmunology 7 (8) (2018), e1452581.

[71] J. Fan, et al., Circulating microRNAs predict the response to anti-PD-1 therapy in non-small cell lung cancer, Genomics 112 (2) (2020) 2063–2071.

[72] H. Zhang, et al., miR-181c contributes to cisplatin resistance in non-small cell lung cancer cells by targeting Wnt inhibition factor 1, Cancer Chemother. Pharmacol. 80 (5) (2017) 973–984.

[73] H. Liu, et al., miR-7 modulates chemoresistance of small cell lung cancer by repressing MRP1/ABCC1, Int. J. Exp. Pathol. 96 (4) (2015) 240–247.

[74] B. Li, et al., MiR-21 overexpression is associated with acquired resistance of EGFR-TKI in non-small cell lung cancer, Lung Cancer 83 (2) (2014) 146–153.

[75] L. Lin, et al., MicroRNA-21 regulates non-small cell lung cancer cell invasion and chemo-sensitivity through SMAD7, Cell. Physiol. Biochem. 38 (6) (2016) 2152–2162.

[76] S. Jiang, et al., MicroRNA-21 modulates radiation resistance through upregulation of hypoxia-inducible factor-1α-promoted glycolysis in non-small cell lung cancer cells, Mol. Med. Rep. 13 (5) (2016) 4101–4107.

[77] M. Garofalo, et al., EGFR and MET receptor tyrosine kinase-altered microRNA expression induces tumorigenesis and gefitinib resistance in lung cancers, Nat Med 18 (1) (2011) 74–82.

[78] K. Kitamura, et al., MiR-134/487b/655 cluster regulates TGF-β-induced epithelial-mesenchymal transition and drug resistance to gefitinib by targeting MAGI2 in lung adenocarcinoma cells, Mol Cancer Ther 13 (2) (2014) 444–453.

[79] J. Rzeszowska-Wolny, et al., Involvement of miRNAs in cellular responses to radiation, Int. J. Radiat. Biol. 98 (3) (2022) 479–488.

[80] Y. Chen, et al., MicroRNA: a novel implication for damage and protection against ionizing radiation, Environ. Sci. Pollut. Control Ser. 28 (2021) 15584–15596.

[81] S. Soares, et al., The influence of miRNAs on radiotherapy treatment in Prostate cancer – a systematic review, Front. Oncol. (2021) 11.

[82] Y. Tang, et al., Radiation-induced miR-208a increases the proliferation and radioresistance by targeting p21 in human lung cancer cells, J. Exp. Clin. Cancer Res. 35 (2016) 7.

[83] Z. He, et al., miR-25 modulates NSCLC cell radio-sensitivity through directly inhibiting BTG2 expression, Biochem. Biophys. Res. Commun. 457 (3) (2015) 235–241.

[84] Y. Li, et al., Knockdown of microRNA-1323 restores sensitivity to radiation by suppression of PRKDC activity in radiation-resistant lung cancer cells, Oncol. Rep. 33 (6) (2015) 2821–2828.

[85] C. Fang, et al., Functional miRNA variants affect lung cancer susceptibility and platinum-based chemotherapy response, J. Thorac. Dis. 10 (6) (2018) 3329–3340.

[86] P.Y. Yip, Phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin (PI3K-Akt-mTOR) signaling pathway in non-small cell lung cancer, Transl. Lung Cancer Res. 4 (2) (2015) 165–176.

[87] W. Jiang, et al., MicroRNA-related polymorphisms in PI3K/Akt/mTOR pathway genes are predictive of limited-disease small cell lung cancer treatment outcomes, BioMed Res. Int. 2017 (2017), 6501385.

[88] M.T. Amjad, A. Chidharla, A. Kasi, Cancer chemotherapy, in: *StatPearls*2022, StatPearls PublishingCopyright ©, StatPearls Publishing LLC, Treasure Island (FL, 2022.

[89] C.P. Wardell, et al., Genomic characterization of biliary tract cancers identifies driver genes and predisposing mutations, J. Hepatol. 68 (5) (2018) 959–969.

[90] C. Auwerx, et al., From pharmacogenetics to pharmaco-omics: Milestones and future directions, HGG Adv 3 (2) (2022), 100100.

[91] N.N. Miteva-Marcheva, et al., Application of pharmacogenetics in oncology, Biomark. Res. 8 (1) (2020) 32.