Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2023**; 28(12): 357
https://doi.org/10.31083/j.fbl2812357

Review

Cellular Senescence in Non-Small Cell Lung Cancer

Huangkai Zhu[1,*,†], Jiaen Sun[2,†], Chong Zhang[2,†], Pei Li[1], Chuntao Tan[3], Minglei Yang[1], Guofang Zhao[1,*]

[1]Department of Thoracic Surgery, Ningbo No.2 Hospital, 315010 Ningbo, Zhejiang, China
[2]Health Science Center, Ningbo University, 315211 Ningbo, Zhejiang, China
[3]Department of Cardiac and Vascular Surgery, Ningbo No.2 Hospital, 315010 Ningbo, Zhejiang, China
*Correspondence: zhuhuangkai21280@163.com (Huangkai Zhu); zhaoguofang@ucas.edu.cn (Guofang Zhao)
[†]These authors contributed equally.

Academic Editor: Amancio Carnero Moya
Submitted: 21 April 2023 Revised: 28 July 2023 Accepted: 8 August 2023 Published: 28 December 2023

Abstract

Lung cancer has the highest mortality rate amongst all malignancies worldwide, and is the second-highest incidence of cancer in women. Non-small cell lung cancer (NSCLC) is responsible for approximately 80% of lung cancer cases. Recent studies indicate that cellular senescence may be a promising cancer biomarker. However, the regulation of cellular senescence and its underlying mechanisms in NSCLC are not yet fully understood. Here, we present a comprehensive analysis of the genes linked to cellular senescence in NSCLC. We also describe the secretory phenotype associated with NSCLC and examine its immune profile and prognostic potential. Our findings offer novel insights into the development of effective NSCLC treatments.

Keywords: cellular senescence; non-small cell lung cancer

1. Introduction

Lung cancer is a particularly aggressive disease and is the leading cause of cancer-related mortality worldwide. There were approximately 2.2 million new cases of lung cancer in 2020 and 1.8 million deaths from this disease [1–3]. Lung cancer is broadly classified into two categories based on the cell types involved, namely non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [4–8]. NSCLC accounts for approximately 80% of cases and is characterized by the presence of anomalous cells that proliferate and metastasize rapidly, usually resulting in poor prognosis and limited therapeutic options [9,10]. NSCLC can be further subdivided into three categories based on histological characteristics, namely adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [11,12]. Adenocarcinoma originates from mucus-producing cells in the respiratory tract lining and is the most frequently observed subtype, accounting for approximately 40% of NSCLC cases [13,14]. Squamous cell carcinoma arises from the cells lining the air passages and accounts for 30% of NSCLC cases [15]. Large cell carcinoma is a less frequent subtype, comprising around 1–3% of all primary lung cancers and usually originating from lung neuroendocrine cells [16]. NSCLC is often asymptomatic during the early stages, thereby posing a challenge for early detection. Common symptoms such as coughing, chest pain, shortness of breath and weight loss are usually experienced at later stages [17]. Smoking is the primary cause of NSCLC, with several other environmental factors also contributing to its development, including exposure to second-hand smoke and radon. Available treatments for NSCLC involve surgery, chemotherapy, radiation therapy, and targeted therapy [18,19]. A better understanding of the molecular mechanisms underlying NSCLC is essential for the development of effective therapies that improve patient outcomes. Of note has been recent research on the involvement of cell senescence in NSCLC.

Senescence is a type of cellular aging and has been investigated as a potential biomarker for cancer [20]. Senescent cells have been observed to accumulate in several cancer types, including NSCLC, and have been linked to tumour growth, resistance to therapy, and unfavourable patient outcomes. Despite these findings, the mechanisms that underlie cell aging in NSCLC remain incompletely understood, with more research needed to clarify the role of senescence in the development and progression of this disease. Senescent cells secrete various molecules that can induce inflammation, angiogenesis and tissue remodelling, thereby facilitating cancer progression. Although there is increasing awareness of the significance of cellular senescence in NSCLC, the factors that regulate this process in cancer cells remain poorly understood. Furthermore, the presence of senescent cells within NSCLC tissue has been linked to unfavourable prognosis and reduced patient survival rates [21]. A better understanding of the role of cellular senescence in NSCLC could therefore have significant implications for the development of new therapies and for more accurate prediction of patient outcomes. It is also important to identify specific senescence markers of aging that could be used in the clinic.

2. Cellular Senescence and NSCLC

Cellular senescence is a biological phenomenon commonly referred to as cell aging and which exhibits multifaceted and intricate involvement in the progression of NSCLC [22]. Some studies have reported that the onset of cell aging can impede NSCLC growth and potentially incite tumour regression. However, other studies have implicated senescent cells within the tumour microenvironment in the progression and metastasis of NSCLC [23,24]. In addition, the presence of senescent cells in NSCLC has been correlated not only with the efficacy of treatments such as chemotherapy and radiotherapy, and also with resistance to these treatments [20,24–29].

2.1 Definiton of Cell Senescence and Its Role in Cancer

Cell senescence is a state of irreversible growth arrest triggered by various stressors, such as DNA damage, telomere shortening, and oxidative stress [30]. By studying inducible changes to the epigenome, Yang *et al*. [31] found that disruption of epigenetic information could lead to aging in mice. On the other hand, restoring the integrity of the epigenome could reverse the signs of aging, suggesting that loss of epigenetic information is a reversible cause of aging. The morphology and metabolism of senescent cells are different to those of normal cells. Senescent cells have a large and flattened cell morphology, increased expression of senescence-associated β-galactosidase (SA-β-Gal), and elevated expression of $p16^{Ink4a}$. These cells remain metabolically active but can no longer divide or proliferate [20]. They secrete a range of inflammatory cytokines and other molecules in what is known as the senescence-associated secretory phenotype (SASP) [32,33]. Cell senescence is a complex process involving multiple molecular pathways, including the *TP53* and $p16^{Ink4a}$/Rb pathways [34,35]. These can be activated by various stressors, leading to the induction of cell senescence. While this is thought to limit the proliferation of potentially cancerous cells, recent evidence suggests senescent cells may also promote cancer by secreting SASP factors that stimulate inflammation and tumour growth. Researchers have sought to understand the role of cell senescence in NSCLC progression and therapy resistance [36]. Accumulation of senescent cells in NSCLC may contribute to disease progression and therapy resistance [24]. Exploiting senescence could therefore potentially be used to improve treatment outcomes [29,37,38].

2.2 Factors Regulating Cell Senescence in NSCLC

Several factors have been identified as key regulators of cell senescence in NSCLC. These encompass genetic alterations, epigenetic modifications, oxidative stress, inflammation, and the tumour microenvironment. For example, genetic alterations such as mutation of the *TP53* tumour suppressor gene are known to promote cellular senescence in NSCLC cells [39,40]. Epigenetic alterations such as DNA methylation and histone modifications can also affect the regulation of cell senescence in NSCLC [41,42]. Furthermore, exposure to environmental toxins such as cigarette smoke can result in oxidative stress, which can in turn induce cell senescence in NSCLC [43]. Inflammation has also been linked to cellular senescence in NSCLC, with pro-inflammatory cytokines such as the chemokine (C-X-C motif) receptor 2 playing a role [44]. Lastly, cell senescence in NSCLC can also be regulated by the tumour microenvironment, which encompasses interactions between cancer cells and stromal cells [24]. The matricellular protein cellular communication network factor 1 (CCN1)/cysteine-rich 61 (CYR61) suppresses NSCLC cell growth by inducing senescence [45].

Regulation of cell senescence in NSCLC is a multifaceted phenomenon that can be influenced by various factors. Comprehensive elucidation of the underlying mechanisms that regulate cell senescence in NSCLC, as well as the identification of effective therapeutic interventions that target this process remain active areas of research. Indeed, further investigations are warranted to gain a deeper understanding of the complexities of this process and to develop potentially novel therapeutic avenues.

3. Genes Associated with Cell Aging in NSCLC

The process of cell aging is multifaceted and involves modifications in gene expression and activity. Multiple genes have been found to exert regulatory effects on cell aging in NSCLC. Elucidation of the molecular mechanisms and identification of the relevant genes that underlie the regulation of cell aging in NSCLC may provide valuable insights into the pathophysiology of this disease and could inform the development of novel therapeutics. Such findings may have implications for the optimization of therapeutic strategies against NSCLC.

3.1 Genetic Mutations and Alterations in NSCLC

NSCLC is a highly heterogeneous disease with a diverse array of genetic mutations and alterations that contribute to its pathogenesis and progression. Among the most frequently mutated genes in NSCLC are *TP53, KRAS, EGFR* and *ALK* [46]. Aberrations to these genes can alter the normal signalling pathways, enhance cell proliferation, and increase resistance to chemotherapy and targeted therapies. The tumour suppressor gene *TP53* plays a critical role in regulating cell cycle arrest and apoptosis in response to DNA damage. *TP53* mutations are present in approximately 50% of NSCLC cases and are associated with poor prognosis and resistance to chemotherapy [47]. Mutations in *KRAS* are found in approximately 15–25% of NSCLC cases and activate downstream signalling pathways, leading to cell proliferation and survival. *KRAS* mutations are associated with resistance to targeted therapies and poor prognosis [48]. *EGFR* mutations are found in approximately 10–15% of NSCLC cases, with a higher inci-

dence reported in non-smokers and Asians [49]. These mutations activate downstream signalling pathways that result in cell proliferation and survival. *EGFR* mutations are associated with sensitivity to *EGFR* tyrosine kinase inhibitors (TKIs) and improved prognosis [50]. *ALK* rearrangements are found in approximately 5–6% of NSCLC cases and activate downstream signalling pathways that lead to cell proliferation and survival. *ALK* rearrangements are associated with sensitivity to *ALK* inhibitors and improved prognosis [51]. Other genetic mutations and alterations in *BRAF, HER2, MET, RET, and ROS1* also contribute to NSCLC pathogenesis and may be targets for novel therapies [52].

3.2 Specific Genes and Pathways Implicated in Cell Aging in NSCLC

Several genes and pathways have been identified as crucial regulators of cell aging in NSCLC. Aberrant regulation of these genes and pathways has been implicated in the development and progression of NSCLC. Understanding their mechanism of action is therefore critical in the development of new therapeutic strategies for this disease. The tumour suppressor gene *TP53* plays a vital role in regulating cell cycle progression and apoptosis [53]. *TP53* mutations are frequently observed in NSCLC and are associated with increased cellular proliferation, decreased apoptosis, and resistance to chemotherapy, all of which contribute to tumorigenesis [54]. Oncogene-induced senescence is a tumour-suppressing defence mechanism [55]. Activation of the ubiquitin-specific proteases 5 (USP5)-Beclin-1 axis is pivotal for overcoming intrinsic *TP53*-dependent senescence in *KRAS*-driven NSCLC development [40]. The matricellular protein CCN1 suppresses NSCLC cell growth by inducing senescence through the *TP53*/*p21* pathway [45]. Short-carbon chain C (2)-ceramide can effectively sensitize paclitaxel(PTX)-induced senescence of NSCLC cells via both $p21^{(waf1/cip1)}$- and $p16^{Ink4a}$-independent pathways [56]. Specific gene expression changes also occur during cellular aging in NSCLC. For example, myeloid zinc finger 1 mediates oncogene-induced senescence by promoting the transcription of $p16^{Ink4a}$ [55]. interferon regulatory factor 8 (IRF8) inhibits *AKT* signalling and promotes the accumulation of $p27^{Kip1}$ protein, resulting in the senescence of NSCLC cells [57]. Homeodomain-only protein homeobox (HOPX) acts as a tumour suppressor in various cancer types. Forced expression of HOPX enhances cellular senescence by activating oncogenic Ras and the downstream mitogen-activated protein kinase (MAPK) pathway in NSCLC [42]. Several other signalling pathways, including *c-Myc*/*HIF-1*α [58], *AKT* [57], and nuclear factor kappa-B (NF-κB) [59] have also been implicated in cellular aging and NSCLC progression. However, further research is needed to fully elucidate the mechanisms by which these genes and pathways contribute to cellular senescence in NSCLC.

4. Secretory Phenotypes Associated with Cell Aging in NSCLC

Cellular senescence is a multifaceted process that involves not only the cessation of cellular proliferation, but also the acquisition of a SASP. This phenotype is marked by the release of various cytokines, chemokines and growth factors, and is known to exert a pivotal role in tissue regeneration. In the context of malignant transformation, the SASP has been linked to cancer progression, immune subversion, and metastatic dissemination. Therefore, understanding the intricate interplay between cellular senescence and the SASP is of paramount importance for devising novel therapeutic strategies that target age-related disorders and cancer.

4.1 SASP and Its Role in Cancer

The SASP is a characteristic hallmark of senescent cells, as well as being present in cancer cells. This phenotype is characterized by the secretion of a diverse array of cytokines, chemokines and growth factors with varied effects on tumorigenesis. SASP is a double-edged sword. On one hand, early SASP is involved in numerous biological processes such as wound healing, immune surveillance, and tissue regeneration. On the other hand, the prolonged existence of SASP can reshape the tumour microenvironment by causing chronic inflammation and thus promoting tumour progression. This can lead to increased tumour vascularisation [60], the promotion of tumour cell migration and metastasis [61], and the induction of epithelial-to-mesenchymal transition of neighbouring cells to promote tumour cell invasion [62].

4.2 Specific SASP Factors Associated with NSCLC

Several specific SASP factors in NSCLC have been reported to play important roles in inducing angiogenesis, invasion, and metastasis [61,63]. The Interleukin-6 (IL-6) cytokine level is increased in the serum of NSCLC patients and is associated with poor prognosis [64,65]. IL-6 promotes the proliferation, migration and invasion of NSCLC cells through activation of the STAT3 signalling pathway. It also inhibits apoptosis and enhances resistance to chemotherapy and radiotherapy. IL-6 has also been shown to induce the expression of angiogenic factors such as VEGF, which promote the formation of new blood vessels and facilitate tumour growth [66]. Interleukin-8 (IL-8) is another cytokine that is frequently upregulated in NSCLC and has also been linked to tumour progression and metastasis [67]. It promotes the proliferation, migration and invasion of NSCLC cells by activating the *AKT* and extracellular regulated protein kinases signalling pathways [68]. Other SASP factors that have been associated with NSCLC include matrix metalloproteinases (MMPs) such as MMP-3 and MMP-9, which are involved in extracellular matrix remodelling and tumour invasion [69]. In addition, chemokines such as Chemokine (C-C motif) ligand 2 pro-

mote the recruitment and polarization of tumour-associated macrophages and eliminate senescent cells, thereby inhibiting cell carcinogenesis [70]. In summary, specific SASP factors play important roles in the development and progression of NSCLC by promoting cell proliferation, migration and invasion, by enhancing angiogenesis and immune suppression, and by contributing to chemotherapy and radiotherapy resistance.

5. Immune Profile and Prognosis of Cell Aging in NSCLC

Immune cells play a critical role in the progression of NSCLC. The immune profile of NSCLC can be influenced by cellular senescence, which has been found to affect prognosis. Recent research suggests that senescent cells in NSCLC stimulate the recruitment of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) into the tumour microenvironment, resulting in immune suppression and tumour progression. Furthermore, these senescent cells release cytokines and chemokines that not only further repress the immune response, but also promote tumour growth [61]. Senescent cells in NSCLC may facilitate the development of an inflammatory microenvironment marked by elevated levels of cytokines such as IL-6 and IL-8, which may further contribute to tumour growth and metastasis [44].

A recent study reported that the poor prognosis of NSCLC was associated with the presence of senescent cells, since these correlated with worse overall patient survival [71]. Senescent cell targeting in a mouse model of NSCLC resulted in a decrease in MDSCs and Tregs in the tumour microenvironment and an increase in effector T cells, leading to reduced tumour growth and improved survival [72]. Therefore, the presence of senescent cells and their secretory phenotype may be closely linked to the immune profile and prognosis of NSCLC. Hence, the targeting of senescent cells and their SASP may be a promising strategy to improve the immune profile and prognosis of NSCLC. The potential for precision oncology in NSCLC is suggested by the underlying mechanism for treatment.

NSCLC is characterized by a complex interplay of genetic alterations, cell differentiation hierarchies, epigenetic modifications, microenvironmental factors, and tumour heterogeneity. The intricate microenvironment is comprised of a diverse population of tumour cells and immune cells, including macrophages, vascular endothelial cells, MDSCs, dendritic cells (DCs), natural killer (NK) cells, and various subtypes of T cells, all of which contribute to a highly heterogeneous niche. Consequently, treatment strategies for NSCLC must take into account the multifaceted nature of this disease, which requires a comprehensive understanding of the interactions between tumour and immune cells within the tumour microenvironment. Further research is needed to identify novel targets and to develop innovative therapies that can modulate the intricate network of signalling pathways and immunological responses in NSCLC, thereby resulting in improved patient outcomes.

5.1 Involvement of the Immune System in NSCLC

NSCLC is known for its capacity to evade the immune system, proliferate, and metastasize throughout the body. Although the immune system has a crucial role in identifying and eliminating malignant cells, NSCLC cells have the ability to evade immune recognition by employing various strategies such as reducing antigen presentation, increasing the expression of immunosuppressive molecules, and recruiting immunosuppressive cells. These evasion mechanisms are believed to contribute to the resistance of NSCLC to immune-based therapies [73].

There has been increasing interest in the use of immunotherapies, such as immune checkpoint inhibitors, to activate the immune system and thus improve the outcome of NSCLC patients [74,75]. Several studies have shown that immunotherapy can improve the survival of NSCLC patients with specific biomarkers, such as high expression of programmed death-ligand 1 (PD-L1), or high tumour mutational burden (TMB) [76]. The relationship between cell aging and immune infiltration in NSCLC has also been investigated [37]. Senescent cells in NSCLC can promote immune evasion and reduce T cell infiltration in the tumour microenvironment through the production of SASP factors, such as IL-6 and IL-8 [77]. Other studies have shown that the immune system may play a role in clearing senescent cells from tissues, suggesting that it may also regulate cell aging in NSCLC [37]. Therefore, a better understanding of the immune profile of NSCLC and its relationship to cell aging could provide important insights for the development of immunotherapies and personalized treatment strategies in NSCLC patients [21,78].

5.2 Effects of Cell Aging on Immune Response in NSCLC

Cell aging has been shown to have a significant impact on the immune response in NSCLC. SASP factors, including IL-6 and IL-8, are known to create an inflammatory microenvironment within the tumour, leading to immune suppression and the escape of cancer cells from immune surveillance [79]. Cell aging can also cause changes in the tumour microenvironment that promote cancer cell growth and suppress immune function [80]. Several studies have indicated that the presence of SASP factors in NSCLC is linked to reduced infiltration of immune cells such as T cells and natural killer cells into the tumour microenvironment. Furthermore, SASP factors can induce the accumulation of immunosuppressive cells, including regulatory T cells and MDSCs, which inhibit immune function [77]. Additionally, cell aging can alter the expression of immune checkpoint proteins, such as programmed cell death protein 1 (PD-1) and PD-L1, thereby inhibiting T cell function [81,82]. Elevated expression of PD-L1 in NSCLC has been

associated with a worse prognosis and reduced response to immunotherapy [83]. Understanding the effects of cell aging on the immune response in NSCLC is therefore, critical for the development of more effective treatment strategies.

5.3 Prognostic Implications of Cell Aging in NSCLC

Emerging evidence suggests the SASP and cell aging may have prognostic value in NSCLC. Indeed, certain SASP factors have been identified as potential biomarkers for poor prognosis in NSCLC patients. Elevated serum levels of IL-6 and IL-8 have for example been linked to reduced overall survival of NSCLC patients [84]. Several studies have also reported that high levels of SASP factors such as IL-6, IL-8, and matrix metalloproteinase-9 (MMP-9) are associated with the poor prognosis and survival of NSCLC patients, while preclinical studies have shown that SASP factors can promote tumour growth and metastasis. Combining these biomarkers with traditional prognostic factors was found to improve the accuracy for predicting patient survival. Furthermore, elevated levels of the SASP factor plasminogen activator inhibitor-1 (PAI-1) have been associated with worse progression-free survival and overall survival of NSCLC patients [85]. These findings highlight the potential utility of SASP factors as predictive biomarkers for NSCLC prognosis and treatment response. However, further research is needed to validate these findings and to identify additional SASP factors with prognostic value in NSCLC.

Specific biomarkers linked to cellular senescence could also serve as valuable predictive tools for therapeutic efficacy in NSCLC patients. Notably, it was reported that elevated levels of histone H2AX phosphorylation (γ-H2AX), a marker for DNA damage, could predict good response to chemotherapy and the survival of NSCLC patients [86]. Another study found that a tumour senescence signature with high expression of $p16^{Ink4a}$, a senescence-associated protein, had significant prognostic value for the overall survival of NSCLC patients [71]. Several methods and biomarkers are currently available for the detection of cellular senescence and for the prediction of patient outcome. However, due to differences at the translational level and the lack of gold standard biomarkers, there is an urgent need for uniform and consistent biomarkers of cellular senescence [37].

6. Therapeutic Implications

6.1 Potential Targets for NSCLC Treatment Based on Cell Aging Mechanisms

Recent advances in our understanding of cell aging mechanisms in NSCLC have led to the identification of potential targets for treatment. One approach is to develop drugs that target specific pathways involved in cell aging, such as the *TP53* pathway or the telomerase pathway [87]. There are currently several ongoing clinical trials in NSCLC patients with *TP53* mutations that target the *TP53* pathway, including PRIMA-1 and APR-246. Another approach currently in the preclinical research phase is to target SASP factors using anti-IL-6 and anti-IL-8 antibodies [88,89]. Using a *KRAS*-mutant mouse model of lung cancer, a combination of MAPK and cyclin-dependent kinase 4/6 inhibitors was found to promote NK cell surveillance by activating SASP components (tumour necrosis factor-α and intercellular adhesion molecule-1), leading to tumour cell death [90].

The identification of predictive biomarkers for treatment response based on cell aging mechanisms is currently also an active area of research. For example, the expression level of specific SASP factors or the presence of certain genetic mutations may be accurate predictive biomarkers for the response to treatment of drugs that target these pathways [91]. The development of targeted therapies based on cell aging mechanisms therefore holds promise for improving the treatment outcomes of NSCLC patients [37]. However, further research is needed to validate these targets and biomarkers, and to test the safety and efficacy of the targeted drugs in clinical trials.

6.2 Current and Emerging Therapies That Target Cell Aging in NSCLC

Recent studies have highlighted the potential of targeting cell aging mechanisms as a novel strategy for NSCLC treatment. Several drugs that target specific pathways involved in cell aging have shown promising results in preclinical and clinical studies. Of note, senolytics are a class of drug that selectively target senescent cells and induce their apoptosis. The senolytic drugs dasatinib [92] and quercetin [93] have shown promising results in preclinical studies of NSCLC [94]. Telomerase inhibitors such as imetelstat and lipid-modified N3′→P5′ thiophosphoramidate oligonucleotide (GRN163L) were found to inhibit the growth of NSCLC cells in preclinical studies [95]. Wang *et al.* [96] reported that bortezomib induced cellular senescence of A549 lung cancer cells by inducing telomere shortening. The mammalian target of rapamycin (mTOR) pathway has also been implicated in the regulation of cell senescence. In preclinical studies, the mTOR inhibitors rapamycin and everolimus were found to induce senescence and inhibit the growth of NSCLC cells [97–99]. Another study reported that the anti-proliferative small molecule ethyl(2-methyl-3-((E)-((naphtha(2,1-b)furan-2-ylca-rbonyl)hydrazono)methyl)-1H-indole-1-yl)acetate) (STK899704) promoted cell death by inducing DNA damage response pathways and senescence after cell cycle arrest [53]. CBP/p300 histone acetyltransferases (HAT) are critical transcription coactivators involved in multiple cellular activities. They appear to act at multiple levels in NSCLC and may therefore represent promising druggable targets. Pharmacological targeting of CBP/p300 drives a redox/autophagy axis that leads to senescence-induced growth arrest in NSCLC cells [100]. Immune checkpoint

inhibitors such as pembrolizumab and nivolumab have also shown promising results for the treatment of NSCLC, particularly in patients with high levels of PD-L1 expression [101]. The targeting of SASP factors such as IL-6 and IL-8 may also enhance the response to immunotherapy. Other targeted therapies that have been investigated in the context of NSCLC and cell aging include Cyclin-dependent kinase (CDK) 4/6 pathway inhibitors, Heat Shock Protein (HSP) 90 inhibitors, and histone deacetylase (HDAC) inhibitors [102]. Furthermore, "one-two punch" sequential treatment provides a therapeutic option to reduce the risk of tumour progression and avoid adverse reactions by eliminating senescent cells induced by conventional anti-cancer treatments such as radiotherapy/chemotherapy [37].

7. Discussion and Conclusion

Lung cancer remains a major contributor to cancer-related mortality worldwide, with NSCLC being the most prevalent subtype. Recently, there has been growing research interest on the role of cellular senescence in the pathogenesis and progression of NSCLC. This comprehensive analysis covers the multiple facets of cellular senescence in NSCLC, including the relevant genes and signalling pathways, secretory phenotypes, immune characteristics, and therapeutic implications.

Cellular senescence is a biological process characterized by the irreversible growth arrest of cells due to diverse cellular stressors [103]. This process has emerged as a potentially useful prognostic and predictive biomarker for cancer, including NSCLC. Numerous genes and pathways have been implicated in cellular senescence in NSCLC, including *TP53*, *CDKN2A* and telomerase. *TP53*, also referred to as the "guardian of the genome", plays a pivotal role in DNA damage response and is frequently mutated in NSCLC. CDKN2A is another tumour suppressor gene that regulates the cell cycle and is frequently inactivated in NSCLC. Telomerase maintains telomere length and prevents genomic instability. It is frequently reactivated in cancer cells, including NSCLC. In addition to the presence of genetic alterations, cellular senescence in NSCLC is associated with the secretion of several pro-inflammatory and pro-tumorigenic factors, collectively known as the SASP. These include a range of cytokines, chemokines, growth factors, and extracellular matrix proteins. Various SASP factors, including IL-6 and IL-8, have been associated with unfavourable prognosis in NSCLC patients.

The pivotal role of the immune system in the development and progression of NSCLC is well established. Emerging evidence now indicates that cell aging can modulate the immune response in NSCLC. Specifically, senescent cells have been shown to promote the infiltration of immunosuppressive cells, including MDSCs and regulatory T cells, into the NSCLC tumour microenvironment, leading to immune evasion and resistance to immunotherapy. However, the induction of senescence has also been reported to enhance the anti-tumour immune response and to improve the efficacy of immunotherapy in NSCLC. Accordingly, the targeting of cell aging in NSCLC represents a promising therapeutic strategy for improving treatment outcomes. Several potential targets have already been identified and include SASP components and the immune system. Notably, inhibition of the SASP factors IL-6 and IL-8 has been found to suppress tumour growth in preclinical models of NSCLC. Immune checkpoint inhibitors that target negative regulators of the immune response have also shown promise in the treatment of NSCLC, especially when combined with senolytic drugs that selectively eliminate senescent cells.

Cell aging is a multifaceted and intricate phenomenon during the development and progression of NSCLC. The involvement of specific genes and pathways, SASP factors and immune factors are all promising areas for further research aimed at improving NSCLC treatment. Future studies should therefore strive to increase knowledge of the underlying mechanisms responsible for cell aging in NSCLC, and to identify and validate robust biomarkers for predicting treatment response. This should allow for the development of more effective strategies that target cell aging in the clinical setting.

Author Contributions

HZ and GZ identified the topic of this manuscript; HZ, JS, CZ, PL, CT, and MY performed the search and analyzed the data from the reviewed literature; HZ, JS, and CZ wrote the manuscript; All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by Ningbo Health Branding Subject Fund, Grant number PPXK2018-05; Ningbo Natural Science Foundation, Grant number 2023J316; Medical Scientific Research Foundation of Zhejiang Province, Grant number 2022KY1138; Science and technology innovation guidance fund project of Hangzhou Medical College, Grant number CX2022006; HwaMei Reasearch Foundation of Ningbo No.2 Hospital, Grant number 2022HMKY37; HwaMei Reasearch Foundation of Ningbo No.2 Hospital, Grant number 2023HMKY20; HwaMei Reasearch Foundation of Ningbo No.2 Hospital, Grant number 2023HMKY32; Ningbo Top Medical and

Health Research Program, Grant number 2022030208; Huadong Medicine Joint Funds of the Zhejiang Provincial Natural Science Foundation of China under, Grant number LHDMD23H160001; China University Industry-University-Research Innovation Fund, Grant number 2022BC078.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] de Sousa VML, Carvalho L. Heterogeneity in Lung Cancer. Pathobiology. 2018; 85: 96–107.
[2] Mao Y, Yang D, He J, Krasna MJ. Epidemiology of Lung Cancer. Surgical Oncology Clinics of North America. 2016; 25: 439–445.
[3] Collins LG, Haines C, Perkel R, Enck RE. Lung cancer: diagnosis and management. American Family Physician. 2007; 75: 56–63.
[4] Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018; 553: 446–454.
[5] Jonna S, Subramaniam DS. Molecular diagnostics and targeted therapies in non-small cell lung cancer (NSCLC): an update. Discovery Medicine. 2019; 27: 167–170.
[6] Nagano T, Tachihara M, Nishimura Y. Molecular Mechanisms and Targeted Therapies Including Immunotherapy for Non-Small Cell Lung Cancer. Current Cancer Drug Targets. 2019; 19: 595–630.
[7] Wang Y, Zou S, Zhao Z, Liu P, Ke C, Xu S. New insights into small-cell lung cancer development and therapy. Cell Biology International. 2020; 44: 1564–1576.
[8] Yang S, Zhang Z, Wang Q. Emerging therapies for small cell lung cancer. Journal of Hematology and Oncology. 2019; 12: 47.
[9] Hsu ML, Naidoo J. Principles of Immunotherapy in Non-Small Cell Lung Cancer. Thoracic Surgery Clinics. 2020; 30: 187–198.
[10] Patel SA, Weiss J. Advances in the Treatment of Non–Small Cell Lung Cancer. Clinics in Chest Medicine. 2020; 41: 237–247.
[11] Dohopolski M, Gottumukkala S, Gomez D, Iyengar P. Radiation Therapy in Non-Small-Cell Lung Cancer. Cold Spring Harbor Perspectives in Medicine. 2021; 11: a037713.
[12] Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, *et al*. Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. 2017; 15: 504–535.
[13] Kim MJ, Cervantes C, Jung Y, Zhang X, Zhang J, Lee SH, *et al*. PAF remodels the DREAM complex to bypass cell quiescence and promote lung tumourigenesis. Molecular Cell. 2021; 81: 1698–1714.e6.
[14] Li X, Zhong M, Wang J, Wang L, Lin Z, Cao Z, *et al*. MiR-301a promotes lung tumourigenesis by suppressing Runx3. Molecular Cancer. 2019; 18: 99.
[15] Niu Z, Jin R, Zhang Y, Li H. Signaling pathways and targeted therapies in lung squamous cell carcinoma: mechanisms and clinical trials. Signal Transduction and Targeted Therapy. 2022; 7: 353.
[16] Ferrara MG, Stefani A, Simbolo M, Pilotto S, Martini M, Lococo F, *et al*. Large Cell Neuro-Endocrine Carcinoma of the Lung: Current Treatment Options and Potential Future Opportunities. Frontiers in Oncology. 2021; 11: 650293.
[17] Simeone JC, Nordstrom BL, Patel K, Klein AB. Treatment patterns and overall survival in metastatic non-small-cell lung cancer in a real-world, us setting. Future Oncology. 2019; 15: 3491–3502.
[18] Alexander M, Kim SY, Cheng H. Update 2020: Management of Non-Small Cell Lung Cancer. Lung. 2020; 198: 897–907.
[19] Miller M, Hanna N. Advances in systemic therapy for non-small cell lung cancer. British Medical Journal. 2021; 375: n2363.
[20] Meng J, Li Y, Wan C, Sun Y, Dai X, Huang J, *et al*. Targeting senescence-like fibroblasts radiosensitizes non-small cell lung cancer and reduces radiation-induced pulmonary fibrosis. Journal of Clinical Investigation Insight. 2021; 6: e146334.
[21] Ferrara R, Naigeon M, Auclin E, Duchemann B, Cassard L, Jouniaux J, *et al*. Circulating T-cell Immunosenescence in Patients with Advanced Non-small Cell Lung Cancer Treated with Single-agent PD-1/PD-L1 Inhibitors or Platinum-based Chemotherapy. Clinical Cancer Research. 2021; 27: 492–503.
[22] Calcinotto A, Kohli J, Zagato E, Pellegrini L, Demaria M, Alimonti A. Cellular Senescence: Aging, Cancer, and Injury. Physiological Reviews. 2019; 99: 1047–1078.
[23] Campisi J. Aging, Cellular Senescence, and Cancer. Annual Review of Physiology. 2013; 75: 685–705.
[24] Zhang B, Fu D, Xu Q, Cong X, Wu C, Zhong X, *et al*. The senescence-associated secretory phenotype is potentiated by feedforward regulatory mechanisms involving Zscan4 and TAK1. Nature Communications. 2018; 9: 1723.
[25] Jiao D, Zheng X, Du X, Wang D, Hu Z, Sun R, *et al*. Immunogenic senescence sensitizes lung cancer to LUNX-targeting therapy. Cancer Immunology, Immunotherapy. 2022; 71: 1403–1417.
[26] Kuilman T, Michaloglou C, Mooi WJ, Peeper DS. The essence of senescence. Genes Dev. 2010; 24: 2463–2479.
[27] Wang M, Morsbach F, Sander D, Gheorghiu L, Nanda A, Benes C, *et al*. EGF Receptor Inhibition Radiosensitizes NSCLC Cells by Inducing Senescence in Cells Sustaining DNA Double-Strand Breaks. Cancer Research. 2011; 71: 6261–6269.
[28] Ge H, Ni S, Wang X, Xu N, Liu Y, Wang X, *et al*. Dexamethasone reduces sensitivity to cisplatin by blunting p53-dependent cellular senescence in non-small cell lung cancer. PLoS One. 2012; 7: e51821.
[29] Chen Y, Zhang C, Jin S, Li J, Dai J, Zhang Z, *et al*. Pemetrexed induces ROS generation and cellular senescence by attenuating TS-mediated thymidylate metabolism to reverse gefitinib resistance in NSCLC. Journal of Cellular and Molecular Medicine. 2023; 27: 2032–2044.
[30] Herranz N, Gil J. Mechanisms and functions of cellular senescence. Journal of Clinical Investigation. 2018; 128: 1238–1246.
[31] Yang J, Hayano M, Griffin PT, Amorim JA, Bonkowski MS, Apostolides JK, *et al*. Loss of epigenetic information as a cause of mammalian aging. Cell. 2023; 186: 305–326.e27.
[32] Chen B, Liang Y, Chen L, Wei Y, Li Y, Zhao W, *et al*. Overexpression of Klotho Inhibits HELF Fibroblasts SASP-related Protumoural Effects on Non-small Cell Lung Cancer Cells. Journal of Cancer. 2018; 9: 1248–1258.
[33] Millar FR, Pennycuick A, Muir M, Quintanilla A, Hari P, Freyer E, *et al*. Toll-like receptor 2 orchestrates a tumour suppressor response in non-small cell lung cancer. Cell Reports. 2022; 41: 111596.
[34] Childs BG, Durik M, Baker DJ, van Deursen JM. Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nature Medicine. 2015; 21: 1424–1435.
[35] Xue W, Zender L, Miething C, Dickins RA, Hernando E, Krizhanovsky V, *et al*. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. Nature. 2007; 445: 656–660.
[36] Tesei A, Arienti C, Bossi G, Santi S, De Santis I, Bevilacqua A, *et al*. TP53 drives abscopal effect by secretion of senescence-associated molecular signals in non-small cell lung cancer. Jour-

nal of Experimental and Clinical Cancer Research. 2021; 40: 89.
[37] Wang L, Lankhorst L, Bernards R. Exploiting senescence for the treatment of cancer. Nature Reviews Cancer. 2022; 22: 340–355.
[38] Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. Journal of Internal Medicine. 2020; 288: 518–536.
[39] Courtois-Cox S, Jones SL, Cichowski K. Many roads lead to oncogene-induced senescence. Oncogene. 2008; 27: 2801–2809.
[40] Li J, Wang Y, Luo Y, Liu Y, Yi Y, Li J, *et al*. USP5-Beclin 1 axis overrides p53-dependent senescence and drives Kras-induced tumourigenicity. Nature Communications. 2022; 13: 7799.
[41] Michalak EM, Burr ML, Bannister AJ, Dawson MA. The roles of DNA, RNA and histone methylation in ageing and cancer. Nature Reviews Molecular Cell Biology. 2019; 20: 573–589.
[42] Chen Y, Yang L, Cui T, Pacyna-Gengelbach M, Petersen I. HOPX is methylated and exerts tumour-suppressive function through Ras-induced senescence in human lung cancer. The Journal of Pathology. 2015; 235: 397–407.
[43] Passos JF, Saretzki G, von Zglinicki T. DNA damage in telomeres and mitochondria during cellular senescence: is there a connection? Nucleic Acids Research. 2007; 35: 7505–7513.
[44] Acosta JC, O'Loghlen A, Banito A, Guijarro MV, Augert A, Raguz S, *et al*. Chemokine Signaling via the CXCR2 Receptor Reinforces Senescence. Cell. 2008; 133: 1006–1018.
[45] Jim Leu S, Sung J, Chen M, Chen C, Cheng J, Wang T, *et al*. The matricellular protein CCN1 suppresses lung cancer cell growth by inducing senescence via the p53/p21 pathway. Journal of Cellular Biochemistry. 2013; 114: 2082–2093.
[46] Tan AC, Lai GGY, Tan GS, Poon SY, Doble B, Lim TH, *et al*. Utility of incorporating next-generation sequencing (NGS) in an Asian non-small cell lung cancer (NSCLC) population: Incremental yield of actionable alterations and cost-effectiveness analysis. Lung Cancer. 2020; 139: 207–215.
[47] Deben C, Deschoolmeester V, Lardon F, Rolfo C, Pauwels P. TP53 and MDM2 genetic alterations in non-small cell lung cancer: Evaluating their prognostic and predictive value. Critical Reviews in Oncology/Hematology. 2016; 99: 63–73.
[48] Wood K, Hensing T, Malik R, Salgia R. Prognostic and Predictive Value in KRAS in Non-Small-Cell Lung Cancer: A Review. JAMA Oncology. 2016; 2: 805–812.
[49] Chapman AM, Sun KY, Ruestow P, Cowan DM, Madl AK. Lung cancer mutation profile of EGFR, ALK, and KRAS: Meta-analysis and comparison of never and ever smokers. Lung Cancer. 2016; 102: 122–134.
[50] Kolesar J, Peh S, Thomas L, Baburaj G, Mukherjee N, Kantamneni R, *et al*. Integration of liquid biopsy and pharmacogenomics for precision therapy of EGFR mutant and resistant lung cancers. Molecular Cancer. 2022; 21: 61.
[51] Du X, Shao Y, Qin HF, Tai YH, Gao HJ. ALK-rearrangement in non-small-cell lung cancer (NSCLC). Thoracic Cancer. 2018; 9: 423–430.
[52] Oxnard GR, Binder A, Jänne PA. New Targetable Oncogenes in Non–Small-Cell Lung Cancer. Journal of Clinical Oncology. 2013; 31: 1097–1104.
[53] Park CW, Bak Y, Kim MJ, Srinivasrao G, Hwang J, Sung NK, *et al*. The Novel Small Molecule STK899704 Promotes Senescence of the Human A549 NSCLC Cells by Inducing DNA Damage Responses and Cell Cycle Arrest. Frontiers in Pharmacology. 2018; 9: 163.
[54] Mogi A, Kuwano H. TP53 Mutations in Nonsmall Cell Lung Cancer. Journal of Biomedicine and Biotechnology. 2011; 2011: 1–9.
[55] Wu D, Tan H, Su W, Cheng D, Wang G, Wang J, *et al*. MZF1 mediates oncogene-induced senescence by promoting the transcription of p16INK4a. Oncogene. 2022; 41: 414–426.
[56] Chen JY, Hwang C, Chen W, Lee J, Fu T, Fang K, *et al*. Additive effects of C2-ceramide on paclitaxel-induced premature senescence of human lung cancer cells. Life Sciences. 2010; 87: 350–357.
[57] Liang J, Lu F, Li B, Liu L, Zeng G, Zhou Q, *et al*. IRF8 induces senescence of lung cancer cells to exert its tumour suppressive function. Cell Cycle. 2019; 18: 3300–3312.
[58] Liu J, Huang X, Liu D, Ji K, Tao C, Zhang R, *et al*. Demethyleneberberine induces cell cycle arrest and cellular senescence of NSCLC cells via c-Myc/HIF-1alpha pathway. Phytomedicine. 2021; 91: 153678.
[59] Xu W, Li Y, Yuan WW, Yin Y, Song WW, Wang Y, *et al*. Membrane-Bound CD40L Promotes Senescence and Initiates Senescence-Associated Secretory Phenotype via NF-kappaB Activation in Lung Adenocarcinoma. Cellular Physiology and Biochemistry. 2018; 48: 1793–1803.
[60] Davalos AR, Coppe J, Campisi J, Desprez P. Senescent cells as a source of inflammatory factors for tumour progression. Cancer and Metastasis Reviews. 2010; 29: 273–283.
[61] Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, *et al*. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumour suppressor. PLoS Biology. 2008; 6: 2853–2868.
[62] Laberge R, Awad P, Campisi J, Desprez P. Epithelial-Mesenchymal Transition Induced by Senescent Fibroblasts. Cancer Microenvironment. 2012; 5: 39–44.
[63] Lee JJ, Perera RM, Wang H, Wu D, Liu XS, Han S, *et al*. Stromal response to Hedgehog signaling restrains pancreatic cancer progression. Proceedings of the National Academy of Sciences. 2014; 111: E3091–E3100.
[64] Liu W, Wang H, Bai F, Ding L, Huang Y, Lu C, *et al*. IL-6 promotes metastasis of non-small-cell lung cancer by up-regulating TIM-4 via NF-kappaB. Cell Proliferation. 2020; 53: e12776.
[65] Liu Y, Gao Y, Lin T. Expression of interleukin-1 (IL-1), IL-6, and tumour necrosis factor-alpha (TNF-alpha) in non-small cell lung cancer and its relationship with the occurrence and prognosis of cancer pain. Annals of Palliative Medicine. 2021; 10: 12759–12766.
[66] Liu C, Yang L, Xu H, Zheng S, Wang Z, Wang S, *et al*. Systematic analysis of IL-6 as a predictive biomarker and desensitizer of immunotherapy responses in patients with non-small cell lung cancer. BMC Medicine. 2022; 20: 187.
[67] Sanmamed MF, Perez-Gracia JL, Schalper KA, Fusco JP, Gonzalez A, Rodriguez-Ruiz ME, *et al*. Changes in serum interleukin-8 (IL-8) levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small-cell lung cancer patients. Annals of Oncology. 2017; 28: 1988–1995.
[68] Wang H, Zhuo Y, Hu X, Shen W, Zhang Y, Chu T. CD147 deficiency blocks IL-8 secretion and inhibits lung cancer-induced osteoclastogenesis. Biochemical and Biophysical Research Communications. 2015; 458: 268–273.
[69] Merchant N, Nagaraju GP, Rajitha B, Lammata S, Jella KK, Buchwald ZS, *et al*. Matrix metalloproteinases: their functional role in lung cancer. Carcinogenesis. 2017; 38: 766–780.
[70] Morein D, Erlichman N, Ben-Baruch A. Beyond Cell Motility: The Expanding Roles of Chemokines and Their Receptors in Malignancy. Frontiers in Immunology. 2020; 11: 952.
[71] Domen A, Deben C, De Pauw I, Hermans C, Lambrechts H, Verswyvel J, *et al*. Prognostic implications of cellular senescence in resected non-small cell lung cancer. Translational Lung Cancer Research. 2022; 11: 1526–1539.
[72] Salminen A, Kauppinen A, Kaarniranta K. Myeloid-derived suppressor cells (MDSC): an important partner in cellular/tissue senescence. Biogerontology. 2018; 19: 325–339.
[73] Chen D, Mellman I. Oncology Meets Immunology: the Cancer-Immunity Cycle. Immunity. 2013; 39: 1–10.
[74] Hellmann MD, Nathanson T, Rizvi H, Creelan BC, Sanchez-

Vega F, Ahuja A, *et al*. Genomic Features of Response to Combination Immunotherapy in Patients with Advanced Non-Small-Cell Lung Cancer. Cancer Cell. 2018; 33: 843–852.e4.
[75] Ricciuti B, Alessi JV, Elkrief A, Wang X, Cortellini A, Li YY, *et al*. Dissecting the clinicopathologic, genomic, and immunophenotypic correlates of KRASG12D-mutated non-small-cell lung cancer. Annals of Oncology. 2022; 33: 1029–1040.
[76] Sabari JK, Leonardi GC, Shu CA, Umeton R, Montecalvo J, Ni A, *et al*. PD-L1 expression, tumour mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Annals of Oncology. 2018; 29: 2085–2091.
[77] Birch J, Gil J. Senescence and the SASP: many therapeutic avenues. Genes and Development. 2020; 34: 1565–1576.
[78] Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nature Reviews Molecular Cell Biology. 2021; 22: 75–95.
[79] Domen A, Deben C, Verswyvel J, Flieswasser T, Prenen H, Peeters M, *et al*. Cellular senescence in cancer: clinical detection and prognostic implications. Journal of Experimental and Clinical Cancer Research. 2022; 41: 360.
[80] Crespo J, Sun H, Welling TH, Tian Z, Zou W. T cell anergy, exhaustion, senescence, and stemness in the tumour microenvironment. Current Opinion in Immunology. 2013; 25: 214–221.
[81] Wang T, Johmura Y, Suzuki N, Omori S, Migita T, Yamaguchi K, *et al*. Blocking PD-L1–PD-1 improves senescence surveillance and ageing phenotypes. Nature. 2022; 611: 358–364.
[82] Onorati A, Havas AP, Lin B, Rajagopal J, Sen P, Adams PD, *et al*. Upregulation of PD-L1 in Senescence and Aging. Molecular and Cellular Biology. 2022; 42: e0017122.
[83] Pan ZK, Ye F, Wu X, An HX, Wu JX. Clinicopathological and prognostic significance of programmed cell death ligand1 (PD-L1) expression in patients with non-small cell lung cancer: a meta-analysis. Journal of Thoracic Disease. 2015; 7: 462–470.
[84] Yasuda T, Koiwa M, Yonemura A, Miyake K, Kariya R, Kubota S, *et al*. Inflammation-driven senescence-associated secretory phenotype in cancer-associated fibroblasts enhances peritoneal dissemination. Cell Reports. 2021; 34: 108779.
[85] Wu K, Zhang X, Li F, Xiao D, Hou Y, Zhu S, *et al*. Frequent alterations in cytoskeleton remodelling genes in primary and metastatic lung adenocarcinomas. Nature Communications. 2015; 6: 10131.
[86] Palla V, Karaolanis G, Katafigiotis I, Anastasiou I, Patapis P, Dimitroulis D, *et al*. Gamma-H2AX: can it be established as a classical cancer prognostic factor? Tumour Biology. 2017; 39: 101042831769593.
[87] Bykov VJN, Eriksson SE, Bianchi J, Wiman KG. Targeting mutant p53 for efficient cancer therapy. Nature Reviews Cancer. 2018; 18: 89–102.
[88] Tan AC, Tan DSW. Targeted Therapies for Lung Cancer Patients with Oncogenic Driver Molecular Alterations. Journal of Clinical Oncology. 2022; 40: 611–625.
[89] Duma N, Santana-Davila R, Molina JR. Non–Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. Mayo Clinic Proceedings. 2019; 94: 1623–1640.
[90] Ruscetti M, Leibold J, Bott MJ, Fennell M, Kulick A, Salgado NR, *et al*. NK cell–mediated cytotoxicity contributes to tumour control by a cytostatic drug combination. Science. 2018; 362: 1416–1422.
[91] Wang M, Herbst RS, Boshoff C. Toward personalized treatment approaches for non-small-cell lung cancer. Nature Medicine. 2021; 27: 1345–1356.
[92] Garmendia I, Pajares MJ, Hermida-Prado F, Ajona D, Bértolo C, Sainz C, *et al*. Yes1 Drives Lung Cancer Growth and Progression and Predicts Sensitivity to Dasatinib. American Journal of Respiratory and Critical Care Medicine. 2019; 200: 888–899.
[93] Lotfi N, Yousefi Z, Golabi M, Khalilian P, Ghezelbash B, Montazeri M, *et al*. The potential anti-cancer effects of quercetin on blood, prostate and lung cancers: An update. Frontiers in Immunology. 2023; 14: 1077531.
[94] Ou H, Hoffmann R, González-López C, Doherty GJ, Korkola JE, Muñoz-Espín D. Cellular senescence in cancer: from mechanisms to detection. Molecular Oncology. 2021; 15: 2634–2671.
[95] Wu X, Smavadati S, Nordfjäll K, Karlsson K, Qvarnström F, Simonsson M, *et al*. Telomerase antagonist imetelstat inhibits esophageal cancer cell growth and increases radiation-induced DNA breaks. Biochimica Et Biophysica Acta (BBA)-Molecular Cell Research. 2012; 1823: 2130–2135.
[96] Wang L, Yin H, Huang S, Huang S, Huang C, Zhang Z, *et al*. Bortezomib induces cellular senescence in a549 lung cancer cells by stimulating telomere shortening. Human and Experimental Toxicology. 2022; 41: 096032712211240.
[97] Tabibzadeh S. Signaling pathways and effectors of aging. Frontiers in Bioscience-Landmark. 2021; 26: 50–96.
[98] Bernard M, Yang B, Migneault F, Turgeon J, Dieudé M, Olivier M, *et al*. Autophagy drives fibroblast senescence through MTORC2 regulation. Autophagy. 2020; 16: 2004–2016.
[99] Cao L, Lee SG, Park S, Kim H. Sargahydroquinoic acid (SHQA) suppresses cellular senescence through Akt/mTOR signaling pathway. Experimental Gerontology. 2021; 151: 111406.
[100] Ansari MSZ, Stagni V, Iuzzolino A, Rotili D, Mai A, Del Bufalo D, *et al*. Pharmacological targeting of CBP/p300 drives a redox/autophagy axis leading to senescence-induced growth arrest in non-small cell lung cancer cells. Cancer Gene Therapy. 2023; 30: 124–136.
[101] Remon J, Vilariño N, Reguart N. Immune checkpoint inhibitors in non-small cell lung cancer (NSCLC): Approaches on special subgroups and unresolved burning questions. Cancer Treatment Reviews. 2018; 64: 21–29.
[102] Shen Z, Wang J, Ke K, Chen R, Zuo A, Zhang R, *et al*. Polyphyllin I, a lethal partner of Palbociclib, suppresses non-small cell lung cancer through activation of p21/CDK2/Rb pathway *in vitro* and *in vivo*. Cell Cycle. 2021; 20: 2494–2506.
[103] Voskamp C, Anderson LA, Koevoet WJ, Barnhoorn S, Mastroberardino PG, van Osch GJ, *et al*. TWIST1 controls cellular senescence and energy metabolism in mesenchymal stem cells. European Cells & Materials. 2021; 42: 401–414.