Literature Review

p21 Genetic Modification as a Tumor-Suppressor Gene: A Future Target in Lung Cancer Therapy?

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Abstract

Lung cancer is one of the leading causes of cancer death worldwide. Although early diagnosis/screening methods and treatment strategies have developed, lung cancer patients' survival rates remain low. However, resistance to chemotherapy and radiotherapy causes tumor recurrence and worsening of the disease, thus being the lead cause of treatment failure. In the growth cycle of lung cancer cells, the highest p21WAF1/CIP1 gene expression was found in early-stage lung cancer and played a role in lung cancer progression. In addition, the correlation between CDK inhibitors and patient survival showed that inactivation of the p21WAF1/CIP1 and p16INK4a genes was associated with lower overall survival and poor prognosis. This review will focus on the role of genetic Modification in lincRNA-p21 in lung cancer therapy and the implication of a combination therapeutic approach.

Keywords: p21WAF1/CIP1, lung cancer, genetic modification therapy

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INTRODUCTION

Lung cancer is one of the most rapidly progressive types of cancer, with a high mortality rate worldwide, with an estimated 1.76 million deaths annually.[1,2] Lung cancer is classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NCSLC is the most frequent form of lung cancer, contributing to 85-90% of all cases. It is divided into squamous cell carcinoma (SQCLC) and adenocarcinoma (ADC), and large cell carcinoma (LCC).[2]

The gradual process of lung cancer caused by the activation of oncogenes and the inactivation of tumor suppressor genes plays an essential role in developing malignant transformation and cancer cells' resistance to therapy. The problem of low overall survival rates of lung cancer patients needs a better concern of lung cancer management. Identification of particular biomarkers, including cell cycle intervention, is required for effective targeted therapy to improve lung cancer patients' prognoses.[1]

CELL CYCLE AND TUMORIGENESIS

Tumorigenesis is associated with abnormal cell proliferation and programmed cell death (apoptosis) disruption.[3] Dysregulation of cell cycle development is the key to cancer cells. The cell cycle is divided into phases: G1, S, G2, and M (mitosis), each regulated by cyclins and cyclin-dependent kinases (CDKs). For example, the G1 phase entering the S phase is regulated by cyclin D/CDK4 and cyclin E/CDK6, and G2 phase to the M phase is regulated by cyclin A/CDK2 and cyclin A/cdc2 (CDK1). Cyclin or CDK activity is regulated by CDK inhibitors and the tumor suppressor protein, p53.[4]

This setting helps determine whether the cell will divide, remain silent, or quiescent (the condition of the cell not dividing but can return to the cell cycle) in response to external stimuli. During the cell cycle, each type of cell has distinct characteristics.

Embryonic stem cells, germ cells, and cancer cells proliferate, but they also undergo cell cycle arrest and go dormant in unpleasant conditions. Cells have a sophisticated management system to synchronize these events. Serious problems such as autoimmune diseases and carcinogenesis can result if these pathways are compromised.[5]

RECENT UPDATES IN LUNG CANCER THERAPY

Chemotherapy is still one of the most commonly used methods for treating malignancies. In general, chemotherapeutic agents contain taxane, platinum, and pemetrexed. Taxane, such as paclitaxel, inhibits microtubules and prevents cell division. Platinum, for example, cisplatin, binds to DNA purines, preventing replication and transcription. Pemetrexed inhibits an enzyme required for synthesizing the essential components of DNA. Targeted therapy, namely tyrosine-kinase inhibitors (TKIs), inhibits constitutive activation of cancer cell kinase signaling pathways and causes cancer cell apoptosis.[2]

The newest class of systemic therapies for cancer are immune checkpoint inhibitors (ICIs), such as pembrolizumab, atezolizumab, and nivolumab, which act via the programmed death ligand 1/2 (PD-L1 and PD-L2) pathway on cancer cells and the programmed death 1 (PD-L2) receptor PD-1) on T cells, where PD-L1 and PD-L2 are thought to suppress the immune system. ICI immunotherapy will prevent suppression of the immune system by cancer cells; as a result, cancer cells are detected by the immune system and undergo cytotoxic death.[6]

Lung cancer therapy depends on the type of cancer, stage, functional status of the patient, comorbidities, and molecular characteristics of the disease.[7] In early-stage SCLC, treatment includes surgery and additional platinum-based chemotherapy or concurrent chemo-radiation. Treatment of SCLC patients with metastases includes systemic chemotherapy with or without immunotherapy.[8]

In NSCLC, surgical resection is the first line at stages I and II, namely surgery at stage IA, surgery with/without chemotherapy at stage IB, and surgery (lobectomy or sub-lobar resection) with chemotherapy at stage II.[9] In patients who cannot be candidates for surgical resection, therapy focuses on stereotactic body radiation therapy (SBRT) or definitive radiotherapy.[7]

Stage III NSCLC tumors cannot be resected, and staging is performed during resection. In stage IIIA, treatment includes adjuvant chemotherapy, although chemotherapy and radiation are the more common options. In stage IIIB, chemotherapy, and radiation are used. In stage IV, therapy includes palliative chemotherapy and radiation. Current NSCLC therapy focuses more on targeted therapy based on mutational status than chemotherapy.[9] For example, in patients with positive epidermal growth factor receptor (EGFR), TKIs such as gefitinib, erlotinib, osimertinib, or afatinib may be used.[7] Other mutations among ROS1, BRAF, RET, TRK, MET, and KRAS genes may be present and specific inhibitors are required for integrated therapy.[9]

p21 GENE AND CANCER CELL

The development of p21 and the Evolution of Cancer Cell

p21 (encoded as the CDKN1A gene) is a CDK inhibitor that inhibits the cell cycle in the G1/S phase and phosphorylation of retinoblastoma proteins. p21 is a commonly used term with various other names, such as cyclin-dependent kinase inhibitory protein-1 [CDKN1A] or $p21^{WAF1/CIP1,}$ due to its diverse functions. At the beginning of its discovery, p21 was identified as a tumor suppressor in various cancer cells, including brain, lung, and colon malignancies, and it was correlated to carcinogenesis and metastasis.[3,5] p21 is a p53 target gene whose expression is promoted by wild-type p53 but not by mutant p53. Hence, p21 is also called wild-type activating factor-1 (WAF1).[5]

Since its early discovery as a CDK inhibitor, p21 has been a critical regulator in various cell processes, including G1/S phase cell cycle development, cell proliferation, DNA damage, and cell damage. The initial study found that p21 binding

to CDK and suppression of CDK interactions with other substrates slowed cell cycle progression in the G1/S phase.[3] In addition, p21 is also correlated to cellular susceptibility to Transforming Growth Factor-beta (TGF-beta), which helps to explain its function in cancer formation—considering the role of TGF-beta in the stages of malignant progression (pre-malignancy phase, malignant development, invasive-dissemination, and metastatic colonization).[5]

Previous research has also demonstrated that the lack of p21 changes keratinocyte proliferation and differentiation and promotes race-tumors' development. p21 is also linked to tumor migration and invasion. Cyclin D1 collaborates with p21 to regulate TGF-beta-mediated cancer cell migration and local tumor invasion. p21-activated kinase (PAK) promotes cancer cell proliferation, migration, and invasion via extracellular signaling and AKT-dependent pathways.[3]

The location of p21 and the state of the p53 protein determines the controversial aspect of p21.[3,5] In pediatric and adult cancers, p53 is the most mutated tumor-inhibiting protein; p53 promotes p21 expression in response to cellular stress to prevent the replication of damaged DNA.[3,5,10] Several circumstances explain why the p21 expression pattern is not p53-dependent on normal tissue growth, cell differentiation, or following serum stimulation.[4] This difference in p21 induction via p53-dependent and p53-independent pathways is specifically related to the role of p21 in tumor development.[3] That said, the effect of p21 on tumor evolution or cancer progression is highly dependent on the status of the p53 protein in cancer cells.[5]

Tumor cells are genomically unstable cells susceptible to mutations that can develop an aggressive phenotype and ultimately lead to metastasis. The pivotal point controls cell cycle progression and is believed to be critical to maintaining genome stability. $P21^{CIP1/WAF1}$ is a CDK inhibitor, so it functions in cell cycle arrest, where P21 can work together or inactivate the cyclin E-CDK2 complex, which plays a role in the cell cycle from G1 to S phase. In addition to its role in cell cycle arrest in the G1/S phase, p21 can also inhibit proliferating cell nuclear antigen (PCNA) during the S phase to slow down DNA synthesis and repair.[10]

Regulation of p53 on p21 makes p21 play a role in inhibiting tumorigenesis; hence p21 is considered an anti-oncogene. Various studies have proved this. In vitro studies have shown that p21 expression negatively affects the malignancy of various cancer cells (skin cancer, TET, adult T cell leukemia [ATLL] by suppressing growth and triggering apoptosis.[5] In vivo studies showed that upregulation of p21 in breast cancer cells led to cell cycle arrest and inhibited the invasion of breast cancer cells. In contrast, the knockdown of p21 increased cell proliferation and suppressed cancer cell invasion.[10] p21 suppresses tumor growth by inhibiting cyclin-kinase complexes, proliferation cell nuclear antigens (PCNA), transcription factors, and coactivators. Otherwise, By reducing the accumulation of DNA damage, p21 may indicate the appearance of tumor evolution, which leads to cancer progression.[5]

Another study in breast cancer cells demonstrated that expression of the cytosolic act-phosphorylated form of p21 (in the cytoplasm) of mouse breast epithelium accelerated tumor progression, suggesting an oncogenic role of cytoplasmic p21 that differs from its anti-proliferative role in the nucleus.[10] Thus, depending on its location, p21 can become an oncogenic or tumor suppressor protein. Controversy about p21 in cancer evolution poses a challenge in determining the right balance in which p21 can play a selective role in inhibiting cancer.[10]

Expression of p21 in Cancer Stem Cells

Several studies have found that p21 expression is associated with resting or late differentiation in tumor cells. p21 was reported to be the main factor for maintaining stem cells/progenitor cells because an increase in p21 mRNA can inhibit the development of progenitor cells. Under normal and stable conditions, large amounts of p21 expression were found in differentiated hematopoietic and red blood cells. Meanwhile,

decreased p21 levels caused the proliferation of hematopoietic stem cells. Therefore, maintaining stem cells in a resting state is very important to prevent premature stem cell depletion.[3,5]

p21 is also related to cancer stem cells (CSC). CSCs are a subpopulation of tumor cells capable of initiating tumors and promoting tumor heterogeneity. CSCs are formed from the accumulation of mutations occurring spontaneously in stem cells and progenitor cells during a person's lifetime. Normal stem cells can become CSC through genetic/epigenetic changes and mutations. CSCs have an excellent ability to self-renewal and maintain their ability to differentiate across multiple lineages. Several studies have shown an association of p21 expression with CSCs in several tumors.[3]

P21 has been reported to attenuate Ras- and c-Myc-dependent epithelial-mesenchymal transition of breast tumors and in vivo attenuates CSC-like gene expression. In prostate cancer, CSC dormancy and recurrence are regulated by bone morphogenetic protein seven via the p38/NDRG1/p21 signaling axis. In ovarian cancer, cell stems are suppressed by p21-regulating mRNA and miRNA. These studies demonstrated the role of p21 in stem cells.[3]

Currently, CSCs in the lung have been extensively studied. According to various studies, the characteristics of pulmonary CSCs include self-renewal ability, multipotent differentiation, tumorigenic potential, expression of stem cell markers, high invasiveness, proliferation as tumor plane, chemoresistance, radioresistance to hypoxia, resistance to apoptosis, and inactivity.[11,12]

The most common hypothesis regarding pulmonary CSCs states that CSCs are formed from tissue-specific normal stem cells in the tissue of origin. However, identifying stem cell origin in the lung is difficult to determine because the epithelium of the trachea and bronchi is quiescent and has a low proliferative fraction. Consequently, cells at specific anatomic sites in the lung were used to simplify the origin of pulmonary CSCs. SQCLC is associated with basal cells in the proximal airways, namely the trachea and bronchi, which exhibit stem cell-like activity. SCLC was associated with Clara cells and neuroendocrine cells, suggesting the presence of stem properties. Meanwhile, ADCs were associated with normal stem cells from the bronchoalveolar branching area.[13]

LincRNA-p21 and Cancer Development

mRNA is a small part of all RNA, with only 3-7% of the total RNA mass in the cell. Nevertheless, mRNA has always been the focus of most of the research. On the other hand, noncoding mRNA has received less appreciation regarding its functional regulatory activity. Although long noncoding RNA (lncRNA) accounts for only a tiny part of the total noncoding RNA (by mass and by the number of molecules), Cancer development has been linked to lncRNA. Long intergenic noncoding RNA-p21 (LincRNA-p21), the target of wild-type p53, is located 15 kb upstream of the p21 gene and regulates gene expression at both transcriptional and post-transcriptional levels. Upregulated by p53, LincRNA-p21 regulates the expression of p53 target genes by physical interaction with heterogeneous nuclear ribonucleoprotein (hnRNP K), which acts as a critical repressor.[5]

LincRNA-p21 regulates cell proliferation, response to DNA damage, and apoptosis through a regulatory role in the expression of p53 target genes. LincRNA-21 maintains reprogramming through several mechanisms; for example, LincRNA-p21 preserves CpG and H3K9me3 methylation in the pluripotency gene promoter, limiting somatic cell reprogramming. LincRNA-p21 also regulates the Warburg effect, so it has an essential role in the metabolism of cancer cells; currently, many research focuses are discussing the role of lincRNA-p21 associated with cancer development. P21-associated noncoding RNA DNA damage-activated (PANDA) is one of the lncRNA located 5 kb upstream of the p21 gene that regulates pro-apoptosis and aging genes through stabilization p53. In response to DNA damage, p53 attaches to the p21 transcriptional start site and activates PANDA and p21 transcription.[5]

p21 Gene-Targeted Therapy Against Lung Cancer

Conventional treatment methods for lung cancer were surgery, chemotherapy, and radiotherapy. However, resistance to chemotherapy and radiotherapy causes tumor recurrence and worsening of the disease, thus being the leading cause of treatment failure. One of the causes of resistance to chemotherapy and radiotherapy is CSC. In addition, the high mutation rate in NSCLC makes therapy more focused on targeted therapy.[14] However, targeted therapy, including TKI, is bound to face resistance and mutations in cell cycle regulators. Therefore, it is essential to focus on cell cycle regulatory genes as a strategy for lung cancer therapy and prevention.[4]

Gene regulation is mainly used for research purposes. Several gene regulatory techniques for manipulating gene expression (knocking out, mutating, or silencing) have been developed:

a. TALENs (transcription activator-like effector nucleases).
b. CRISPR (clustered regularly interspaced short palindromic repeats).
c. rAAV (recombinant adeno-associated virus).
d. ZFNs (zinc finger nucleases).
e. Homologous recombination.
f. Small interference RNA using lentivirus or adenovirus infection.

To study tumor growth, apoptosis, and cell cycle arrest in cancer cells, several versions of p21 have been created in vitro and in vivo models. Gene editing to alter the amount of p21 expression can be used as an additional therapy to suppress carcinogenic characteristics or inhibit treatment resistance in specific cancers.

p21, in general, has two roles closely related to the development of cancer cells. Research that discusses the function of p21 as a tumor suppressor was carried out in a study by B. Shamloo et al.[5] The survey results using a p21-deficient mouse model proved to be susceptible to the formation of hematopoietic, epithelial, and endothelial tumors. Another study also showed that p21-deficient mice injected with the carcinogen azoxymethane showed faster growth of premalignant lesions. Reverse proofing by transduction of adenovirus to increase p21 gene expression in prostate cancer cells has proven that the p21 gene can induce apoptosis and decrease tumor size in mice. The same results were shown by performing an in vitro test on cervical cancer cells that could not increase after p21 overexpression. Cell proliferation and tumor growth decreased significantly after introducing p21 and p53 via nanoparticle injection into a mouse model. These findings highlight the complexities of p21 in cancer therapy and the significance of a multimodal therapeutic strategy.[5]

p21 has an essential role in regulating G1/S and G2; therefore, p21 plays a role in cancer therapy.[3] An increase in p21 causes the cessation of the cancer cell cycle in the G1 or G2/M phase to stop the cell cycle.[5] Research with epigenetic Modification of p21 using histone hypermethylation method showed a significant picture in inhibiting the development of lung cancer cells. The expression of the p21 gene has been reported as a clinical marker of tumor progression. The resulting increase in protein levels indicates a higher overall survival rate in lung cancer patients.

Conversely, the results show that rapid tumor progression is associated with lower levels of p21 in patients with thoracic malignancies. We have seen in vitro studies on cancer cells modified with lentiviral infection. Research conducted using short hairpin RNA to suppress the SKP2 gene proved effective in increasing the expression of the p21 gene.[15]

Based on research conducted by Zhao et al.,[16] it is known that p21 is needed in NSCLC therapy to increase sensitivity to gefitinib. In human ovarian cancer cells, p21 increases the cytotoxic effect of cisplatin, while in hepatoma cells, exogenous p21 expression inhibits cell growth and increases cisplatin sensitivity.[3]

In the growth cycle of lung cancer cells, overexpression of cyclin D1 and underexpression of $p16^{INK4a}$ at an early stage were found to have a significant effect on poor prognosis. The $p21^{WAF1/CIP1}$ gene expression was generally decreased in advanced lung cancer, whereas the highest

expression was found in early-stage lung cancer. In addition, the association between CDK inhibitors and patient survival showed that inactivation of the $p21^{WAF1/CIP1}$ and $p16^{INK4a}$ genes was associated with lower overall survival and poor prognosis.[4]

Research on the CDK inhibitor gene targeting the p16 gene was carried out to see the mechanism of action of cell cycle arrest due to increased p21 expression. In tumor cells with fast progression, increased expression of p21 will affect cell growth and prevent proliferation.[17] A study was conducted to determine the effect of the p21 gene by inhibiting the TCAB1 gene in lung cancer cells. TCAB1 is one of the structural and essential component proteins in NSCLC. The role of TCAB1 in tumors is related to impaired telomere function and impaired mRNA formation. Overexpression of TCAB1 promotes cancer cell proliferation, while suppression of the TCAB1 gene will inhibit cancer cell growth by inducing growth arrest and cell development and stimulating apoptosis. In vitro experiments against TCAB1 gene suppression effect on increasing p21 levels in A549 cells (lung adenocarcinoma). Increasing p21 levels in cells that do not have the TCAB1 gene causes cancer cells to become senescent and unable to divide.[18]

Furthermore, previous studies have been conducted to prove that the p21 gene is required in the senescence and apoptosis of cancer cells in vitro. The expression of p21 in this study was produced indirectly by suppressing the miR-34a gene. miR-34a is a tumor suppressor inhibitor implicated in many tumors, including lung tumors. So far, its regulation is related to the p53 gene, but in this study, it was found that p53 levels were not directly related to miR-34a but had a different relationship with p21. Briefly, these results suggest that miR-34a might upregulate p21 and tell that p21 is a major effector of the induction of senescence and apoptosis of NSCLC cells.[19]

CONCLUSION

Lung cancer is one of the most diagnosed cancers and the leading cause of cancer death worldwide. Although early diagnosis/screening methods and treatment strategies have developed, lung cancer patient survival remains low. The development of more efficient therapeutic targets is needed to improve patient prognosis. Lung cancer therapy depends on the type of cancer, stage, functional status of the patient, comorbidities, and molecular characteristics of the disease. Traditional treatment methods for lung cancer include surgery, radiotherapy, and chemotherapy. However, resistance to chemotherapy and radiotherapy causes tumor recurrence and worsening of the disease, thus being the leading cause of treatment failure. One of the causes of resistance to chemotherapy and radiotherapy is CSC. In addition, the high mutation rate in NSCLC makes therapy more focused on targeted therapy.

$P21^{CIP1/WAF1}$ is a CDK inhibitor, so it stops the cell cycle and can be an oncogenic or tumor suppressor protein. P21 is also associated with Cancer stem cells (CSC). As a CDK inhibitor, P21 has an essential role in the cell cycle, where an increase in P21 causes the arrest of the cancer cell cycle in the G1 or G2/M phase, thereby stopping the cell cycle. In the growth cycle of lung cancer cells, the highest $p21^{WAF1/CIP1}$ gene expression was found in early-stage lung cancer and decreased in advanced lung cancer. The association between CDK inhibitors and patient survival rates also showed that inactivation of the $p21^{WAF1/CIP1}$ and $p16^{INK4a}$ genes was associated with lower overall survival and poor prognosis. Various studies have shown that increased p21 expression, which is generated indirectly through the p16 gene and suppression of the TCAB1 protein and miR-34a gene, indicates that increased p21 expression prevents proliferation and induces senescence and apoptosis of NSCLC cells. Therefore, the function of p21 in stopping the cell cycle is expected to become a more efficient target therapy for lung cancer.

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