Review Paper:

The Role of TP53 Mutations in Lung Cancer: Molecular Mechanisms, Therapeutic Implications and Future Directions

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Abstract

Lung cancer is the most common in the world with multifaceted and diverse molecular etiology. Lung cancer initiation, progression and metastasis are orchestrated by a network of enzymes and proteins. They include TP53, KRAS, EGFR and ALK, which are expressed and mutated at abnormally high levels. These molecules control signaling in various cellular pathways including growth, survival, differentiation and invasion.

This review focuses on the malignantly regulated TP53, which is commonly and mutated most frequently in non-small cell lung cancer Overall, we also highlighted the role of TP53 in lung cancer development, the existing therapeutic approaches against TP53 and its relation about the efficacy and adverse events such as resistance and side effects and the next steps to achieve better outcomes in TP53 -positive lung cancer patients.

Keywords: TP53, NSCLC, Mutation, Mechanism, Inhibitors.

Introduction

Lung cancer is considered the primary contributor to cancer-related deaths on a worldwide scale, as 18% of cancer-related fatalities each year.[19] Lung cancer kills over a million people annually and is undoubtedly one of the main causes of cancer death globally, according to the International Agency for Research on Cancer.[24] Compared to statistics from 1980 which indicated that only 31% of lung cancer cases were reported in developing Nations, the current scenario shows a significant increase, with the majority (55%) of cases now being prevalent in these countries.[21] Based on the study conducted in Europe, lung cancer is the main cause of cancer-related fatalities and emerges as third prevalent tumor in both genders.[35]

Lung cancer patients still have a poor prognosis despite advancements in detection and treatment; in the United States, only 15% of patients survive for more than 5 years following analysis.[60] Smokers have a 20-fold increased risk of lung cancer compared to non-smokers and tobacco usage is directly responsible for 85%–90% of lung cancer cases.[3] Non-small cell lung carcinoma is one of the subtypes of lung cancers, comprises around 80% of lung malignancies and presents distinct clinical and pathological features compared to small cell lung carcinoma (SCLC). Adenocarcinoma (AC), constitutes 40-50% of all lung cancer cases, stands as the most common subtype within non-small cell lung cancer which comprises of SQCC and LCLC. LCLC can now be diagnosed as adenocarcinoma or neuroendocrine tumor, according to genetic analysis.[17] Consequently, screening high-risk groups for lung cancer early has been shown to be the most successful strategy for lowering patient death.

Chest pain, coughing and difficulty in breathing are some of the signs of lung tumor.[16] TP53, often known as the "guardian of the genome," is a tumor protein that is important for sustaining genomic integrity and also preventing the creation of malignancy, by controlling how genes are expressed and triggering arrest of cell cycle, repairing damaged DNA, or programmable cell death (apoptosis). The influence of TP53 respond to cellular stress and DNA disruption, which permits damaged cells to multiply and pick up new mutations, eventually encourages tumor development and metastasis. TP53's relevance in lung tumors is highlighted by its widespread mutation and correlation with stronger tumor behaviors, resistance to treatment and worse outcomes for patients.

As a result, there is a pressing need for targeted medicines that restore or improve TP53 activity in lung cancer. Strategies aimed against mutant TP53 or its downstream effectors are being intensively researched as prospective therapeutic options to increase treatment effectiveness and patient outcomes in lung cancer. Therefore, this review aims to provide comprehensive information regarding various perspective of TP53 in lung cancer progression.

Lung cancer epidemiology

Epidemiology of lung tumor changing as a result of variables includes urbanization, industrialization and environmental pollution, making it a serious worldwide health concern.[33] There are several factors that can contribute to lung cancer carcinogenesis, but smoking has been shown to be one of the main ones. Although it is a known fact that 15% of lung cancer patients are never smokers.[55] Lung cancer risk factors also include exposure to things like air pollution, occupational carcinogens and pollution from burns from cooking and poor diet.[57]

Signaling pathways involved in lung cancer: Recently, cellular networks and signaling pathways are well recognized to be essential for carrying out and regulating significant pro-survival and pro-growth cellular activities.

As a result, they are primarily responsible for the start of cancer as well as prospective treatments for it. Lung cancer frequently exhibits dysregulation of these pathways, which results in the overexpression or mutation of important molecules.[49] Development of protein kinase inhibitors targeting B-RAF, AKT1, PI3K and ERK pathways improves the lung cancer treatment stratagies[8] and align cascades in response to extracellular and internal cues to regulate the development, reproduction and survival of cells[4]. Many common tumor types have been activated by means of phosphoinositide 3-kinase (PI3K) and RAS, which regulate associated signaling pathways. It has now been demonstrated that PI3K inhibitors reduce tumor size in transgenic mice cancer models.

Protiens responsible for lung cancer disease: Lung malignancy might serve as therapeutic targets or biomarkers.[54] Furthermore, it has been observed that lung cancer formation and progression are linked to the over-activation of protein kinase AKT, indicating that this protein may have therapeutic potential.[53] Mutations in the TP53 gene have a significance role in the onset and spread lung cancer, especially in (NSCLC).[56] They also have an impact on prognosis and respond to targeted treatment in NSCLC with EGFR mutations.[37]

Importance of tp53 in lung cancer: The TP53 gene, a tumor suppressor protein is essential for sustaining genomic stability, integrity and limiting cancer formation.[32] TP53 has been related to reproductive control in addition to cancer, indicating that it has a larger influence on human health.[6] TP53 mutations in non-small cell lung cancer (NSCLC) are related with a poor prognosis and resistance to chemotherapy as well as radiation.[7] TP53 mutations also influence the outcome and response to targeted treatment in EGFR-mutated NSCLC.[22]

Mutation of TP53: TP53 is the frequently mutated gene in human cancer, typically causes production of length defective amino acids with oncogenic gain of functions.[9] However, the relevance of these mutations is unclear, with some being neutral alterations that are co-selected during oncogenic transformation.[42] TP53 mutations are linked to increased instabilities and altered gene expression, resulting in a poor clinical prognosis in numerous cancer types.[11] Important mutations of TP53 are displayed in table 1.

Drug currently used in the targeting of TP53: In order to cure lung cancer, TP53 has been the target of several drugs such as PRIMA-1 and PRIMA-1MET, which give mutant p53 characteristics similar to those of the natural type[2]. A190, is a promising chemical that causes the NEDD9 gene to be overexpressed and restores mutant p53 function.[48] Furthermore, TOP-53, a derivative of podophyllotoxin, has shown strong anticancer efficacy against lung cancer and lung metastatic cancer.[51] Collective drug information specifically for TP53 and its mode of action on TP53 are arranged in table 2.

Limitation of drugs used in targeting TP53: Lung cancer medication therapy presents several drawbacks. Repurposed medications, particularly those administered via inhalation, have shown promise as a viable alternative according to Yuan et al[58]. The limited success of systemic chemotherapy and surgery underscores the necessity for innovative treatment modalities such as targeted therapies[14]. However, drug resistance poses challenges in targeted therapy, particularly in NSCLC, necessitating more specialized medicine approach. Despite significant advancements in medication therapy for lung cancer, aggregate research findings indicate that critical issues remain unresolved.

Role of tyrosine kinase enzymes: Tyrosine kinase enzymes are proteins that control many biological activities play including cell development, cell proliferation and differentiation. Tyrosine kinase enzymes play vital role in the genesis and development of lung tumor.[30] Both emphasize the role of receptor tyrosine [6] kinases, like EGFR and ALK, in this process. The abnormal activation of these kinases can cause "oncogene addiction" and susceptibility like crizotinib. However, resistance to tyrosine kinase inhibitors (TKIs) is a prevalent concern, proposing that cancer stem cells may be involved[36]. Tyrosine kinase receptors as diagnostic, prognostic and therapeutic tools in lung cancer, emphasizing the necessity for more study in this field.

Table 1
Important mutations of TP53 and its types

S.N.	Mutation	Position	Mutation Type
1	11333C>A	11333	Silent[28]
2	11339G>A	11339	Silent[31]
3	11370C>T	11370	Missense[34]
4	378C>G	378	Nonsense[46]
5	7578406C>T	7578406	Silent[13]
6	c. G >A10987	10987	Deletion[45]
7	c. T >A13365	13365	Deletion[45]
8	184G>T	184	Deletion[29]
9	248C>T	248	Deletion[23]
10	249G>T	249	Missense[44]

Table 2
Currently used Small molecular inhibitor targeting TP53

S.N.	Drug	Action on TP53
1	APR-246 (Eprenetapopt, PRIMA-1MET)	p53 mutation reactivation[5]
2	RITA	p53 mutation reactivation[47]
3	MDM2 inhibitors (e.g. Nutlin-3)	Inhibition of MDM2-p53 interaction[59]
4	HDM2 antagonists (e.g., RG7112)	Inhibition of MDM2-p53 interaction[15]
5	Tenovins (e.g. Tenovin-1)	Reactivation of mutant p53[26]
6	SCH529074	Inhibition of MDM2-p53 interaction[25]
7	Prima-1	Reactivation of mutant p53[41]
8	PhiKan083	Reactivation of mutant p53[52]
9	STIMA-1	Reactivation of mutant p53[38]
10	CP-31398	Stabilization and activation of p53[27]
11	PK11007	Reactivation of mutant p53[10]
12	P53 peptide aptamer	Inhibition of MDM2-p53 interaction[43]
13	MI-219	Inhibition of MDM2-p53 interaction[40]
14	Tanshinone IIA	Reactivation of mutant p53[1]
15	MIRA-1	Reactivation of mutant p53[18]

Table 3
Showing limitations of certain drugs against tp53 in body

S.N.	Drug	Side Effects
1	APR-246 (Eprenetapopt, PRIMA-1MET)	Nausea, vomiting, diarrhea, fatigue, headache[8].
2	RITA	Gastrointestinal discomfort, fatigue, headache, Hepatotoxicity, hematological abnormalities, cardiac toxicity[47].
3	MDM2 inhibitors (e.g. Nutlin-3)	Dizziness, vomiting, diarrhea, tiredness, headache, neutropenia, anemia, liver and heart damage[59].
4	HDM2 antagonists (e.g. RG7112)	Nausea, vomiting, diarrhea, fatigue, headache, neutropenia, thrombocytopenia, liver toxicity[15].
5	Tenovins (e.g. Tenovin-1)	Gastrointestinal discomfort, fatigue, headache, hematological abnormalities, liver toxicity[26].
6	SCH529074	Nausea, vomiting, diarrhea, fatigue, headache, liver toxicity, cardiac toxicity[25].
7	Prima-1	Gastrointestinal discomfort, fatigue, headache, hematological abnormalities, liver toxicity[41].
8	PhiKan083	Nausea, vomiting, diarrhea, fatigue, headache, hematological abnormalities, liver toxicity[52].
9	STIMA-1	Nausea, vomiting, diarrhea, fatigue, headache, myelosuppression[38].
10	CP-31398	Gastrointestinal discomfort, fatigue, headache, hematological abnormalities, liver toxicity, cardiac toxicity[27].
11	PK11007	Nausea, vomiting, diarrhea, fatigue, headache, hematological abnormalities, liver toxicity, cardiac toxicity[10].
12	P53 peptide aptamer	Nausea, vomiting, diarrhea, fatigue, headache, hematological abnormalities, liver toxicity, cardiac toxicity[43].
13	MI-219	Gastrointestinal discomfort, fatigue, headache, hematological abnormalities, liver toxicity, cardiac toxicity[40].
14	Tanshinone IIA	Gastrointestinal discomfort, headache, myelosuppression[20].
15	MIRA-1	Gastrointestinal discomfort, fatigue, headache, hematological abnormalities, liver toxicity, cardiac toxicity[50].

Future Perspectives

Numerous research pathways could augment our comprehension and management of TP53-positive lung cancer. Primarily, conducting thorough genomic profiling and molecular characterization of pulmonary neoplasms could facilitate the identification of biomarkers indicative of TP53 mutation status and reaction to targeted therapeutic approaches. Moreover, employing cutting-edge model systems in preclinical investigations, such as patient derived organoids and genetically modified murine models, may elucidate the intricate interplays between TP53 modifications and the neoplastic microenvironment.

Additionally, the exploration of innovative therapeutic modalities, including gene editing tools and immunotherapies directed towards TP53 neo antigens, showed potential in surmounting drug resistance and enhancing long term prognosis in patients afflicted with TP53-positive lung carcinoma. Collaborative endeavors involving researchers, clinicians and pharmaceutical enterprises will be imperative in translating these discoveries into clinically significant progressions for the well-being of individuals with TP53-driven lung cancer.

Conclusion

Lung malignancy remains important global health challenge due to high diverse molecular landscape, with TP53 emerging as a pivotal player in its pathogenesis, particularly in NSCLC. Despite the development of therapeutic strategies targeting TP53 and its downstream effectors, challenges such as drug resistance and toxicity persist, limiting their efficacy. However, with ongoing research and advancements in understanding TP53 biology and tumor microenvironment interactions, there is hope for improved clinical outcomes in TP53-positive lung cancer patients.

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