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AN OVERVIEW ON EARLY DETECTION OF LUNG CANCER VIA PD-L1 PATHWAY BY USING INSILICO METHODS

Ch. Bhavani*[1], Kummari Aparna[2], Moduaru Tejo Arun, [2] Madishetti Abhishek Murthy[2], Tadikonda Rama Rao[3]

[1]Assistant Professor, Department of Pharmaceutics, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India.

[2]CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India.

[3] Professor and Principal, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana India.

*Corresponding Author : Ch. Bhavani Assistant Professor, Department of Pharmaceutics, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India.

ABSTRACT:

According to the American Cancer Society (2023), non-small cell lung cancer (NSCLC) makes up the majority of lung cancer cases, which are a major cause of cancer-related mortality globally. Lung cancer survival and prognosis are greatly increased by early detection. The immune checkpoint protein programmed death-ligand 1 (PD-L1) is a vital biomarker and therapeutic target that is involved in tumor immune evasion (National Cancer Institute, 2023). In silico techniques, such as machine learning, molecular docking, and bioinformatics, provide quick, easy, and affordable means of comprehending PD-L1 dynamics and improving lung cancer early detection. This study addresses the promise of computational methods in early PD-L1-based diagnoses as well as the etiology, epidemiology, and treatment of lung cancer.

Keywords:

Lung cancer, NSCLC, molecular docking, gene expression, PD-L1 pathway, biomarker, Insilco analysis.

1) Introduction:

The fact that lung cancer is often detected at an advanced stage makes it one of the most deadly and aggressive malignancies in the world(1).NSCLC accounts for over 85% of all instances of lung cancer (American Cancer Society, 2023). In tumor immune evasion, the PD-L1/PD-1 pathway is a key immunological checkpoint(2).Prompt detection of PD-L1 expression can result in more accurate diagnosis and tailored treatment(3).Because they make it possible to model intricate biological systems and analyze large amounts of data quickly, in silico methods are transforming oncology(4).Bronchogenic carcinoma, another name for lung cancer, is the leading cause of cancer-related death worldwide. It arises in the bronchi or lung parenchyma. Global health systems are still greatly impacted by it, even with improvements in diagnosis and treatment.(5)

***There are two main categories of the disease*:**

• Non-small cell lung cancer (NSCLC), which includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounts for around 85% of all cases of lung cancer.(6)

• About 15% of cases are Small Cell Lung Cancer (SCLC), which has a rapid development and metastatic rate and is associated with a history of smoking.(7)

2) Etiology:

Lung cancer is a complex disease that develops due to a combination of hereditary and environmental factors. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two main classifications; NSCLC makes up about 85% of all cases (8).

- **Smoking tobacco:**

Worldwide, tobacco use continues to be the primary cause of lung cancer. Among the more than 60 carcinogens found in cigarette smoke are nitrosamines and polycyclic aromatic hydrocarbons (PAHs), which damage DNA and cause mutations in important tumor suppressor and oncogene genes (9). According(10), smoking is responsible for 85–90% of lung cancer fatalities, and the risk grows exponentially with prolonged exposure.Because of carcinogen-induced mutagenesis, smokers are more likely to have mutations in TP53, KRAS,andEGFR(11).

- **Exposures in the Workplace and Environment:**

Exposure to environmental toxins raises the risk of lung cancer even in nonsmokers.The second most common cause of lung cancer and a significant risk factor for non-smokers is radon gas, a naturally occurring radioactive gas (12).Asbestos, silica dust, diesel exhaust, and other industrial pollutants are known occupational carcinogens (13).Asbestos exposure, in particular, is linked to both lung cancer and mesothelioma, and has a synergistic effect with smoking.

- **Pollution of the Air**:

Lung cancer risk is greatly increased by long-term exposure to nitrogen oxides from industrial and vehicular emissions, as well as particulate matter (PM2.5 and PM10), particularly in urban populations (14). PM2.5 and outdoor air pollution are categorized as Group 1 carcinogens by the International Agency for Research on Cancer (IARC).

➢ **Genetic Predisposition**:

Large-cell carcinoma.About 15% of cases are small cell lung cancer (SCLC), which is distinguished by its quick growth and early metastases (20).Additionally, genetic predisposition is involved, especially in patients with non-smoking and early-onset lung cancer.Increased risk has been linked to polymorphisms in genes implicated in carcinogen metabolism, such as CYP1A1, GSTT1, and NAT2 (15).Even after controlling for smoking, the risk is increased by 1.5 to 2.5 times if there is a family history of lung cancer.

➢ **Infections with viruses**:

Lung carcinogenesis has been linked to oncogenic viruses including Epstein-Barr Virus (EBV) and Human Papillomavirus (HPV), especially in Asian females who do not smoke (16). Immune suppression and oncogene activation may result from viral incorporation into host genomes.

➢ **Long-Term Lung Conditions**:

It has been demonstrated that underlying respiratory diseases such as pulmonary fibrosis, TB, and chronic obstructive pulmonary disease (COPD) raise the risk of lung cancer, most likely as a result of tissue remodeling and persistent inflammation (17).New therapeutic approaches have been developed as a result of major progress in the last five years in understanding the function of the PD-1/PD-L1 pathway in non-small cell lung cancer (NSCLC).

➢ ***Key causes include: -***

- **Tobacco Smoking**: The leading risk factor, responsible for 85-90% of lung cancers (American Cancer Society, 2023).
- **Environmental Pollutants**: Radon gas, asbestos, arsenic, and air pollution.
- **Occupational Exposure**: Exposure to carcinogens in industries like mining and construction.
- **Genetic Predisposition**: Inherited mutations and family history.
- **Chronic Lung Diseases**: COPD, pulmonary fibrosis, and prior lung infections.

3) Epidemiology:

Analysis of Lung Cancer Epidemiology.Lung cancer continues to be the world's top cause of cancer-related fatalities and a major public health concern. Lung cancer caused about 2.2 million new cases and 1.8 million deaths, or 11.4% of all new cancers and 18% of all cancer deaths worldwide, according to the GLOBOCAN 2020 estimations (18).Worldwide Distribution.Globally, lung cancer is the third most prevalent cancer to be diagnosed in women and the most common in males.North America, Central and Eastern Europe, and Eastern Asia have the highest incidence rates (19).Due to rising tobacco use and a lack of diagnostic resources, the burden of disease is moving to low- and middle-income nations.According to Histological Type,Two main categories can be used to broadly classify lung cancer:NSCLC, or non-small cell lung cancer, is responsible

for about 85% of instances. Among the subtypesare:Adenocarcinoma (the most prevalent kind overall).Squamous cell carcinoma.

- **Rate by Age and Gender:**

Due to increased smoking rates, men have historically had a higher incidence of lung cancer. However, due to shifting smoking habits, the prevalence among women has been increasing in several nations, particularly in high-income areas (21).Most cases of lung cancer are discovered after the age of 65, and the disease primarily affects older persons.Non-Smokers' Lung Cancer.Even while smoking is still the greatest risk factor, 10–25% of incidences of lung cancer, especially in Asian women, happen to people who have never smoked, suggesting the presence of additional risk factors such as: Genetic vulnerability,PM2.5,or air pollution,Occupational exposures to radon,EBV and HPV are examples of viral infections (22).

- **Mortality and Survival:**

Due primarily to late-stage detection, the 5-year survival rate for lung cancer is still low, ranging between 15% and 20% worldwide (21).Survival is greatly increased by early detection: the 5-year survival rate for localized stage lung cancer is above 60%, while the 5-year survival rate for metastatic disease is less than 10% (23).

4) The PD-L1 Pathway in Lung Cancer:

The programmed death-ligand 1 (PD-L1) pathway plays a central role in the regulation of immune responses within the tumor microenvironment and is particularly significant in lung cancer progression and immune evasion**.** PD-L1, also known as CD274**,** is a transmembrane protein expressed on tumor cells, dendritic cells, and macrophages, and is a key immune checkpoint molecule (25).

- **Mechanism of Action:**

PD-L1 binds to its receptor PD-1 (programmed cell death protein 1) on activated T cells**,** resulting in the inhibition of T-cell proliferation, cytokine production**,** and cytotoxic activity**.** This binding essentially turns off the immune response against tumor cells, allowing cancer to grow and evade immune surveillance (26).Tumors exploit this mechanism by upregulating PD-L1 expression**,** often in response to interferon-γ in the tumor microenvironment. This is especially relevant in non-small cell lung cancer (NSCLC)**,** where high PD-L1 expression is observed in a substantial proportion of patients (27).

5) PD-L1 as a Biomarker in Lung Cancer:

One of the most clinically important biomarkers of lung cancer, especially non-small cell lung cancer (NSCLC), is programmed death-ligand 1 (PD-L1). By attaching to its receptor, PD-1, on activated T cells and preventing anti-tumor immunity, PD-L1, a member of the B7 family of immune checkpoint proteins, plays a crucial part in tumor immune evasion (3).PD-L1 functions as both of the following types of biomarkers:Regardless of treatment, a prognostic biomarker forecasts the overall result.A predictive

biomarker is one that shows the possibility of a response to a certain treatment, particularly immune checkpoint inhibitors (ICIs).

- **Immunotherapeutic Predictive Value:**

Better clinical response to PD-1/PD-L1 inhibitors, such as the following, is linked to high PD-L1 expression in tumor cells:
Pembrolizumab,

Nivolumab,

Atezolizumab,

Durvalumab.

Pembrolizumab's usefulness as companion diagnostic biomarker was established inKEYNOTE-024, where first-line treatment with the drug significantly increased survival inNSCLC patients with PD-L1 expression ≥50% (32).

- **Evaluation Methods:**

Immunohistochemistry (IHC) is the main method used to evaluate PD-L1 employing particular assays:22C3 (for pembrolizumab) pharmDx,Assay for SP142 (atezolizumab),Assays for SP263 and 28-8.The tumor proportion score (TPS), which measures the fraction of tumor cells expressing PD-L1, is assessed by these tests.In Silico and Non-Invasive Evaluation.Liquid biopsies and new in silico techniques seek to predict PD-L1 expression non-invasively:PD-L1 mRNA levels can be estimated by transcriptomic analysis utilizing TCGA and RNA-Seq data (5).PD-L1 status can be inferred from CT/PET imaging features using radiogenomics and machine learning.Exosomal PD-L1 and circulating tumor DNA (ctDNA) are being researched as substitutes for tissue biopsies (35).Clinical Significance PD-L1 is still a vital biomarker for:Therapeutic decision-making (e.g., first-line use of ICIs.Stratification in clinical trials,Personalized immunotherapy strategies.

6) Conculsion:

The PD-L1 pathway plays a critical role in lung cancer progression through its immune evasion mechanisms, and its overexpression has made it a key biomarker for both diagnosis and therapeutic decision-making, particularly in non-small cell lung cancer (NSCLC)**.** As immunotherapy becomes an increasingly standard component of lung cancer treatment, the accurate detection and interpretation of PD-L1 expression is essential for personalized medicine**.** Traditional tissue-based assessment methods, while effective, are limited by invasiveness, heterogeneity, and temporal variability. In this context, in silico approaches—including molecular docking, transcriptomic analysis, bioinformatics modeling, and machine learning—offer significant advantages for the non-invasive prediction, validation, and targeting of PD-L1**.** These methods enable high-throughput screening of candidate molecules, virtual biomarker profiling, and simulation of protein-ligand interactions, accelerating the discovery of novel diagnostic agents and improving patient stratification for immune checkpoint therapy.By integrating PD-L1 pathway insights with cutting-edge computational tools, researchers and clinicians can enhance the early detection of lung cancer, optimize immunotherapy outcomes,

and advance toward more precise, predictive, and personalized cancer care. Continued innovation in in silico modeling, combined with experimental validation, will be key to fully unlocking the clinical potential of PD-L1 and similar immune-related biomarkers in oncology.

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