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Introducing PROTAC Therapy—a Novel Tailored Approach to Lung Cancer Treatment

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Abstract:

Drug resistance in cancer is a major challenge to properly treating malignancy. Therapies aimed at proteins involved in cancer development may become less effective due to acquired resistance to medications, often resulting from mutations as well as heightened expression of the targeted proteins. Posttranslational modifications (PTMs) like as phosphorylation, methylation, ubiquitination, and acetylation are crucial for regulating protein expression levels. PROTACs are engineered to selectively degrade a specific protein of interest (POI) by ubiquitination, resulting in a regulated decrease in the POI's expression. PROTACs show great potential in targeting hitherto untargetable proteins, such as various transcription factors. PROTACs enhance antitumor immune therapy by specifically modifying certain proteins. Although molecular therapies have advanced, lung cancer remains a major contributor to cancer-related mortality. The management of those with lung cancer is now limited by a lack of targeted therapy choices and the development of acquired drug resistance. Using the intracellular ubiquitin-proteasome system for directed protein breakdown might enhance individualized treatment for lung cancer patients. This study explores the rationale for using PROTAC therapy as an innovative specific therapy and the current advancements in PROTAC development for lung tumors.

INTRODUCTION

Cancer incidence and death rates are on the rise globally, with lung tumors being the most often detected kind, representing 11.6% of all cases. The malignancy of the lung is the primary cause of cancer-related deaths worldwide, accounting for 18.4% of all cancer fatalities and resulting in substantial societal and economic impacts. The five-year survival rate for lung cancers is below 20%. Early-stage lung cancer individuals who had micro-invasive carcinoma and carcinoma had a 5-year survival rate above 100%, whereas advanced-stage lung cancer patients had a survival rate of around 2% (3). Patients with advanced-stage lung cancer should be given a thorough diagnosis and be prioritized for chemotherapy or radiation. Timely detection of lung cancer and appropriate therapy may significantly enhance patients' survival rate by 20%. Smoking is responsible for about eighty percent of fatalities related to lung cancer (4). Factors contributing to the chance of developing lung cancer include exposure to radon, asbestos, long-term and repeated contact to air pollutants, including emissions of polycyclic aromatic hydrocarbons (PAH), and a previous history of cancer of the lungs. The World Health Organization (WHO) categorizes lung cancers into two primary groups: non-small cell lung cancer (NSCLC) representing 80–85% of cases, and small cell lung cancer (SCLC) accounting for the remaining 15%. NSCLC may be classified as adenocarcinoma (LUAD), squamous cell carcinoma (LUSC), and large cell carcinoma (LCC) (5). Every subclass may be subdivided into many groups based on the molecular targetable genetic profile. The 5-year rate of survival for metastatic lung cancer, including both NSCLC and SCLC types, are around 4% (5). Attempts have been made to classify histological subtypes of lung cancer. Each subtype, including adeno, squamous, and small cell carcinoma, has diverse genetic characteristics as identified by the Cancer Genome Atlas via molecular analysis (6). This variety complicates the interpretation

of comprehensive therapy studies that combine clinical outcomes and can miss important therapeutic options designed for specific mutational backgrounds (6).

Both TNM staging and thorough genes are essential for choosing the treatment for patients having lung tumors. Patients undergo biopsy, staging, and genome sequencing to determine suitable therapies for lung tumors, such as surgical removal, radiation, systemic radiation therapy, specific treatment, and immunotherapy. Many individuals with advanced cancer are likely to have tumor development over time as a result of the clonal selection of treatment-resistant tumor cells. Developing innovative strategies to address medication resistance is essential for improving patient results (7).

Although advancements have been made in identifying driver mutations, the outlook for patients with advanced or metastatic NSCLC remains unfavorable. The primary obstacle associated with targeted treatment is the development of acquired resistance (8). Typical resistance mechanisms involve of changes in driving oncogenes, variations in parallel signaling pathways, histologic transformations, and drug tolerance (9). The requirement for innovative treatments that address both the primary mutation and probable resistance pathways is underscored by the resistance and subsequent advancement seen in several individuals. One innovative treatment approach involves the application of target protein degraders (TPD) such proteolysis targeting chimeras (PROTACs) or lysosomal-targeting chimeras (LYTACs). LYTACs and PROTACs use intrinsic cellular mechanisms to specifically eliminate cancer-causing proteins (10). The PROTAC approach is currently employed in laboratory experiments, animal studies, and early-stage clinical trials to evaluate its efficacy against key alterations in various cancer types (11). This study presents the PROTAC innovation, explores advancements in PROTAC innovation for lung cancer, and assesses the potential and obstacles in using PROTACs for clinical applications to improve lung tumor therapy.

Introduction proteolysis targeting chimera

PROTACs are molecules with two different functions that use the natural ubiquitin-proteasome system to target and eliminate certain proteins associated with illnesses like cancer (12). PROTACs are composed of two protein binding molecules that are covalently bonded. One molecule attaches to the protein targeted for degradation, while the other engages the E3 ubiquitin ligase, facilitating ubiquitination and subsequent destruction (13). Proteins are ubiquitinated and then degraded by the proteasome via a process including activation, conjugation, and ligation steps. Ubiquitin is transferred in a step-by-step manner from E1 to E2 and ultimately to the target protein for degradation by the E3 enzyme. Proteasomes break down the protein (14). The PROTAC molecule exploits this mechanism by attaching to the ubiquitin-E2-E3 complex and the desired protein, promoting ubiquitination and eventual degradation of the protein (14). The PROTAC addresses several resistance-related difficulties by fully degrading the protein. Additionally, the PROTAC does not need contact with the active region of the molecule. PROTAC compounds may expedite the breakdown of several target molecules and may need lower dosages compared to direct inhibitors (15). This might result in less systemic adverse effects as compared to direct inhibitors. This approach is rapidly progressing and is being studied in several kinds of malignancies including lung, breast, prostate, and hematologic cancers. The modular structure of PROTAC design provides significant potential, flexibility, and effectiveness in creating new PROTACs to target and break down different intracellular protein substrates (16). Small chemicals that bind to specific regions of target proteins are used in PROTAC development as ligands for the protein-of-interest (POI), rather than conventional small molecule inhibitors (SMIs) that need high affinities to block protein function. Various PROTACs have been created and improved by using a range of small molecule substances, including authorized by the Food and targeted inhibitors, failed clinical trial medicines, and tool compounds (17). For instance, small molecule epidermal growth factor receptor (EGFR) inhibitors and ALK inhibitors were used to create PROTACs that specifically target and destroy EGFR and ALK (18).

Many reported PROTACs use commonly expressed CRBN and VHL E3 ligases, potentially resulting in on-target toxicity (19). PROTACs targeting the same protein exhibit different degradation rates when using either a CRBN or a VHL E3 ligase. Identifying E3 ligases that are unique to tumors and developing specific ligands for them might greatly enhance the effectiveness of tumor-targeted therapies. PROTACs have numerous advantages as compared to conventional small molecule inhibitors (SMIs) (20). PROTACs function by degrading protein targets rather than by limiting their activity. This is expected to provide better suppression in a scenario where the cancer-causing behavior of an objective may happen regardless of its enzymatic function. PROTACs may modify the scaffolding role of certain proteins to enhance the effectiveness of the payloads and overcome tolerance (21). It may target and dismantle multicomponent complexes of proteins that are often considered “undruggable” since blocking one subunit may not deactivate the complex’s function. Furthermore, PROTACs might combat resistance by degrading overexpressed proteins of interest induced by small molecule inhibitors or proteins of interest arising from mutations in the targets (22). PROTACs

have unique event-driven pharmacology, allowing them to trigger many cycles of degradation, unlike SMIs that depend on occupancy-driven pharmacology. PROTAC molecules provide a unique mechanism that enables them to degrade a range of target proteins using minimum drug dosages to achieve the desired medical result. The modular design of PROTACs allows for convenient and adaptable development and enhancement (23).

Advancements in PROTAC technology

PROTACs have become innovative treatments for lung cancer and effective approaches to combat medication resistance in recent times. Several PROTAC medicines have been created to target established goals for therapy in NSCLC, including EGFR, KRAS, ALK, BRAF, and BCL-XL (23). These medications have shown anti-cancer effectiveness in cultured cells and experimental tumor models. Additional improvement of these PROTAC medicines is necessary, coupled with thorough preclinical assessment before advancing to clinical trials.

PROTACs that target EGFR

The main EGFR mutations are EGFREx19Del and EGFRL858R. First and second-generation EGFR-TKIs, including as gefitinib, erlotinib, afatinib, and dacomitinib, were created for targeting these genetic variants directly (24). Osimertinib addressed resistance problems by specifically targeting the EGFRT790M mutation that developed as a result of previous EGFR-TKIs (25). Many patients who first benefit from osimertinib will eventually develop resistance owing to additional EGFR alterations, structural alterations, and heightened MET amplification. Approximately 40% to 50% of patients had novel EGFR mutations, namely in the C797, G796, and L718 sites, leading to cancer recurrence due to resistance to treatment. The majority of advanced-stage patients with lung cancer have reduced effectiveness of EGFR-TKIs due to resistance, emphasizing the requirement for innovative treatment approaches to combat acquired resistance mechanisms such the emergence of new EGFR C797S and T790M mutations (26). PROTAC approach efficiently targets EGFR mutations that are resistant by inducing the degradation of specific EGFR mutants (27). Molecule 4, a PROTAC compound created from afatinib, caused the breakdown of the gefitinib-resistant L858R/T790M mutant EGFR in the H1975 cell line. This work showed that PROTACs may effectively degrade mutant EGFR proteins located on the cell membrane to address drug-resistant EGFR mutations. Building upon this finding, many research teams have created innovative EGFR PROTACs, with some showing effectiveness in inhibiting tumor growth in animal models. The Zhang group has developed accessible EGFR PROTAC, HJM-561, to address treatment resistance in NSCLC resulting from EGFR triple mutations. This drug effectively targets mutant EGFR proteins, showing potent antitumor effects in cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) mice with EGFR Del19/T790M/C797S mutations that did not respond to osimertinib therapy (28). The Zhu group developed potent covalent inhibitors using dacomitinib to target and destroy EGFR (29). The Li group discovered two powerful and selective compounds, 13a and 13b, that target a specific protein and efficiently inhibited the development of malignancies in a laboratory setting (30). CFT8919 has been shown to cause tumor shrinkage in preclinical tumor models that are resistant to first-, second-, and third-generation EGFR-TKIs. It also has the ability to target CNS metastases in the preclinical model (31). These EGFR PROTACs show great promise as candidates for future development and evaluation in clinical research as new treatments to address EGFR-TKI-induced resistance.

PROTACs that target KRAS

Mutations in the KRAS gene have a critical role in the pathogenesis of multiple malignancies. The most common mutation is the KRASG12C (32). Investigators have been working to develop KRAS inhibitors for a long time. KRAS mutations result in a molecule that remains in a very persistent state of activity because of its robust interaction with GTP (33). Protacs designed to target KRAS aim to overcome resistance in KRAS12C and other KRAS mutations. In 2020, the Bond group revealed the initial KRAS PROTAC designed for the KRASG12C (34, 35). The PROTACs utilized ARS-1620 to attach to KRASG12C and thalidomide derivatives, aiming to eliminate the KRAS G12C mutant via CRBN E3-ligase (36). The Crews group developed VHL-based PROTACs by using MRTX849 as the covalent KRASG12C warhead. Their main chemical LC-2 induced the degradation of KRAS and impeded the MAPK signaling pathway, resulting in reduced p-ERK levels across multiple human lung cancer cell lines with the KRASG12C mutation. Nevertheless, this PROTAC did not demonstrate superior antiproliferative activity compared to MRTX849, perhaps because of its covalently permanent character that disrupts the usual catalytic process seen in PROTACs (36).

Focusing on ALK with PROTACs

Anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase belonging to the insulin receptor kinase subfamily, was first discovered via a chromosomal translocation associated with anaplastic large cell lymphoma (ALCL), a form of T-cell non-Hodgkin's lymphoma (37). The discovery of ALK gene

rearrangement represents a significant advancement in treating NSCLC, which makes up approximately eighty percent of those with lung cancer. ALK is essential for brain development since it has a substantial influence on certain neurons in the nervous system. Crizotinib (Xalkori) is the first ALK inhibitor authorized by the FDA for treating patients with metastatic nonsmall cell lung cancer that is ROS1+ or ALK+ (39). Drug resistance and the initiation of a relapse phase during crizotinib treatment have been attributed to mutations located in the ALK kinase domain. There is a scarcity of inhibitors that possess the capability to impede the extensive array of ALK mutants. Cittatinib, the second ALK blocker approved by the FDA, blocks several mutations that cause resistance to crizotinib (40). The subsequent approvals included brigatinib, alectinib, and others (39). In rare instances, inflammatory myofibroblastic tumors manifest in internal organs and soft tissues, such as the brain, pancreas, mouth, epidermis, breast, nerve, gastrointestinal and genitourinary tracts, bone, stomach, kidney, urinal bladder, and ovary. Lorlatinib, a third-generation ALK inhibitor, successfully blocks frequent resistance variants including ALKG1269A and ALKL1196M. However, its effectiveness is compromised by dual alterations like ALKL1196M/D1203N, ALKF1174L/G1202R, and ALKC1156Y/G1269A (41, 42). Ongoing research is focused on developing PROTACs that selectively target mutant ALK due to the many permanent changes seen in ALK-positive NSCLC. Mammalian cells typically have a limited spread of ALK mRNA and protein, which remain at a modest level in adult individuals. Pharmacologically degrading ALK with SNIPER or PROTAC should not cause intolerance in humans based on ALK's physiological role in mammals (43). Hence, it is anticipated that ALK degraders/disruptors, small molecule agents with dual functionalities to breakdown or interrupt ALK, would have minimal negative impacts on clinical health.

Targeting of FAK targeting

A cytoplasmic tyrosine kinase, focal adhesion kinase (FAK) regulates cellular proliferation and signal transductions mediated by integrins. FAK activation is seen in NSCLC with KRAS mutations (44). In vitro, D-PROTAC lowered the FAK protein levels in A427 cells, a KRAS mutant NSCLC cell line, in a dose-dependent manner, resulting in over 90% degradation. For the purpose of treating A427 cells, either defactinib or D-PROTAC was utilized (45). Significantly larger potency characterized D-PROTAC than defactinib. Cell viability was observed to diminish by 70% upon exposure to D-PROTAC. Conversely, treatment with defactinib led to a viability reduction of 24% (46, 47). Furthermore, cell migration and invasion were substantially inhibited by D-PROTAC in comparison to defactinib. Analyzed in vivo investigations used mice with xenograft A427 tumors that were treated with intratumor injections of D-PROTAC or 10 mg/kg defactinib. Following a 21-day period, the tumor volume in the D-PROTAC group escalated by 340 mm3 from its initial value of 100 mm3. In contrast, the defactinib group witnessed a rise of 1500 mm3. In the D-PROTAC group, there was an 89% decline in FAK levels, whereas the reduction observed in the defactinib group was only marginal (47). In the absence of significant damage to neighboring healthy tissue, D-PROTAC appears to be biosafe.

DISCUSSION AND FUTURE PROSPECTS

Targeting tumor therapy has significantly transformed the treatment of various kinds of cancer over the last twenty years. However, the effectiveness of these therapies is often restricted by the emergence of drug resistance. Comprehending the most recent resistance pathways might result in creating advanced medication generations to improve therapeutic effectiveness in people (48). Yet, the increasing expenses and technological challenges associated with combating drug resistance might render this approach unfeasible in the long run. Therefore, there is an urgent requirement to create new therapeutic protocols and treatment approaches. PROTAC technique has revolutionized drug development by providing several benefits compared to traditional protein inhibitors based on occupancy (49). PROTACs are being created for targeting several clinically significant targets, with over a dozen of them progressing to clinical trials, showcasing the significant potential of this novel therapeutic approach. As seen in the instances provided, PROTACs provide an efficient method to combat different types of developing drug resistance to SMIs (50). Due to their event-driven pharmacology, PROTACs are effective in removing the target protein completely and inducing its degradation through target binding rather than disrupting its function. This makes them suitable for treating various mechanisms of resistance generated by target therapy in clinical settings (51). This involves processes such as binding of drugs hindered by small genetic alterations leading to continuous concentrate stimulation, mutations that modify the structure of the binding domain, acquisition of scaffolding activity due to target complex reorganization, overexpression of target proteins, increased competition from natural ligands, and splicing mutations (52).

Overall, PROTACs show promise in addressing the many obstacles encountered in targeted treatments due to drug resistance. PROTAC technology has significant drawbacks, such as the risk of cancer cells developing resistance to PROTACs over time, which has garnered interest from both academics and business (53). The

mechanisms of resistance seen in small molecule inhibitors (SMIs) might also appear in proteolysis-targeting chimeras (PROTACs) due to changes in both the Protein of Interest (POI) or the E3 ligase, which could hinder the formation of a ternary complex by the PROTAC. The medicine's resistance was not generated by mutations disrupting the binding to the Protein of Interest (POI), but rather by genetic modifications that hinder the fundamental components of the Ubiquitin-Proteasome System (UPS) (54). The mutants have mutations impacting the ubiquitination process, leading to varying resistance depending on the specific E3 ligase targeted by the PROTAC (55, 56). Despite the potential development of resistance, PROTACs show increasing promise in disease treatment because to their advantages over standard SMIs, especially in their capacity to quickly provoke resistance in tumors (57). It is premature to determine whether these commitments will result in tangible advantages in medical therapies. We expect to see evidence of concept results from these research shortly due to the current clinical trials and the release of new drugs for testing. Enhancing our capacity to forecast potential drug resistance mechanisms in advance allows us to develop tactics to avoid, impede, or overcome such resistance. PROTACs may be advantageous in reducing resistance since opposition to a VHL-recruiting PROTAC does not always mean resistance to a CRBN-recruiting PROTAC, and vice versa (59). Over 600 E3 ligases in the human genome will be identified, resulting in the discovery of new E3 ligases and ligands suitable for PROTAC development. Using a variety of E3 recruiters may assist preserve therapeutic efficacy and lower the chances of resistance, resulting in the creation of stronger and more efficient treatments for various cancers (60).

CONCLUSION

PROTACs, as a group, have less than ideal physical and chemical properties that hinder their development in the pharmaceutical field. It is essential to evaluate where the PROTACs are located in the lung tissue to treat lung cancer effectively. Additionally, PROTACs have pharmacodynamic effects that go beyond their pharmacokinetics, requiring the development of suitable pharmacodynamic biomarkers to determine dosing regimens. Additional study is needed to ascertain the optimal method of integrating PROTAC technology with existing anti-cancer therapies to achieve the highest clinical efficacy. Novel diagnostic tests are required to evaluate the efficacy of PROTAC in lung tumor xenograft models and immunocompetent animals at preclinical stages, both in laboratory settings and living organisms. Over the last two decades, molecular oncology medicines have heavily concentrated on lung cancer. Ongoing experimental and early clinical trials of a growing range of PROTAC candidates aim to promote customized and targeted treatment for enhancing the prognosis for individuals with advanced lung cancer.

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