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Application and Development of Targeted Drugs for Cancer

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Abstract. Cancer remains one of the leading causes of mortality worldwide, with its incidence continuing to rise. Traditional treatment modalities, including surgery, radiotherapy, and chemotherapy, though effective in some cases, are often limited by systemic toxicity, low specificity, and the emergence of resistance. The advent of molecular-targeted therapies has revolutionized cancer treatment by enabling precision medicine approaches that selectively inhibit tumor-associated molecular pathways. EGFR tyrosine kinase inhibitors (EGFR-TKIs) have significantly improved survival outcomes in lung cancer patients. However, acquired resistance and high drug costs, as seen with third-generation inhibitors such as Osimertinib, pose persistent clinical challenges. This review provides a comprehensive overview of the mechanisms of action, clinical applications, and resistance pathways of current targeted therapies in oncology. Furthermore, it highlights emerging molecular targets and explores future directions for enhancing therapeutic efficacy and overcoming resistance through integrated molecular and mechanical strategies.

Keywords: Target identification, drug resistance, multi-target drugs, cancer

1. Introduction

Cancer has emerged as a critical global public health challenge, characterized by high morbidity and mortality rates. Despite advancements in traditional therapies—such as chemotherapy, radiotherapy, and surgical interventions—these approaches often suffer from significant drawbacks, including high systemic toxicity, low tumor specificity, and the development of resistance. In recent decades, progress in molecular biology and genomics has paved the way for targeted cancer therapies, offering a paradigm shift toward more precise and individualized treatment strategies.

Targeted therapies act by selectively inhibiting molecular pathways essential for tumor cell proliferation, survival, or angiogenesis. Common clinical agents include epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), anaplastic lymphoma kinase (ALK) inhibitors, MET inhibitors, and anti-angiogenic agents. While these therapies have demonstrated substantial efficacy, they are often accompanied by adverse effects across multiple organ systems, such as dermatologic toxicity, gastrointestinal disturbances, pulmonary injury, and cardiotoxicity [1].

Recent studies have further revealed that cancer progression is not solely driven by genetic and epigenetic alterations but also involves mechanical interactions between tumor cells and their microenvironment. For instance, gene ontology (GO) analyses have identified functional roles for targets such as ACVRL1, NTRK3, and CDK1 in regulating cell motility and mechanical stress

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responses. Notably, despite the identification of numerous candidate targets—including VEGFR, PDGFR, MEK, PI3K, and others—tumor progression involves multi-omics complexity, encompassing mutations, methylation, copy number variation, and non-coding RNA regulation. This complexity limits the utility of expression-based analyses alone [2]. Therefore, a comprehensive understanding of tumor biology that integrates molecular signaling with the mechanical dynamics of the tumor microenvironment may offer novel avenues for targeted therapy design, including the repurposing of existing drugs and development of combinatorial strategies.

2. Potential target drugs for lung cancer

In recent years, several molecular targets have emerged as promising candidates for therapeutic intervention in lung cancer, particularly small cell lung cancer (SCLC). Among these, key proteins involved in DNA repair, apoptosis, cell cycle regulation, and immune modulation are of particular interest.

AAK (Aurora A Kinase) plays a role in regulating the cell cycle and apoptosis by interacting with c-MYC. Arixetinib, an oral AAK inhibitor, has demonstrated therapeutic potential through the induction of cell cycle arrest. Clinical studies suggest that AAK inhibitors may enhance anti-tumor efficacy when used alone or in combination with chemotherapy agents [3].

ATR (ataxia telangiectasia and Rad3-related protein) is a crucial regulator of the S-phase checkpoint during DNA replication. ATR inhibitors have shown anti-tumor activity in patients with previously treated SCLC, particularly when combined with agents such as topotecan or irinotecan. Combination regimens have demonstrated good tolerability and safety profiles in early-phase clinical trials (e.g., NCT02487095 and NCT02595931).

PARP (poly ADP-ribose polymerase) inhibitors target DNA damage repair pathways, which are often upregulated in SCLC. Temozolomide, although not formally approved, is frequently used in clinical practice and has shown significant efficacy in recurrent SCLC, especially in patients with brain metastases. Combination therapy with PARP inhibitors, such as veliparib, can help reverse temozolomide resistance and improve overall response rates, as shown in the NCT01638546 trial [4].

WEE1, a cell cycle-related kinase downstream of ATR/ATM, is also overexpressed in SCLC. WEE1 inhibitors are under investigation for their ability to sensitize tumors to DNA-damaging agents by disrupting G2/M checkpoint control.

DLL3 (Delta-like ligand 3) is another notable target, as it is highly expressed in SCLC but not in normal adult tissues, making it an attractive therapeutic candidate. Treacilib, approved by the FDA in 2021 for extensive-stage SCLC (ES-SCLC), has shown a median overall survival (OS) of 5.4 months in relapsed/refractory settings. AMG757, a bispecific T-cell engager antibody targeting DLL3 and CD3, has exhibited promising preclinical results and is currently undergoing a Phase I clinical trial (NCT03319940). Additionally, DLL3-targeted therapies have demonstrated synergistic benefits when combined with irinotecan in clinical trials (e.g., NCT03098030), improving OS to 6.9 months.

Ganglioside targets, such as those modulated by BMS-986012 (a fucosyl-GM1 monoclonal antibody) and datuximab (an anti-GD2 antibody), are also being explored due to their overexpression in SCLC and association with metastatic potential. These agents are primarily being evaluated in the relapsed/refractory setting.

CD47, which interacts with the SIRPα receptor on macrophages to inhibit phagocytosis, has emerged as an immune checkpoint of interest. The CD47 inhibitor TIT-621 has shown potential in enhancing macrophage-mediated tumor cell clearance and is currently in Phase I trials.

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TIGIT (T cell immunoreceptor with Ig and ITIM domains) suppresses cellular immunity and has become a promising target in immunotherapy. Tiragolumab, a TIGIT antibody, is in Phase III clinical development (NCT04256421) in combination with atezolizumab and the EP chemotherapy regimen for first-line treatment of ES-SCLC.

Lastly, Bcl-2, an anti-apoptotic protein often overexpressed in SCLC, can be targeted using inhibitors such as APG-1252. Early-phase trials have shown this agent to be effective with manageable adverse effects, such as transient thrombocytopenia, without significant hematotoxicity [5].

Together, these targeted and immunomodulatory strategies represent a multi-faceted approach to SCLC treatment, with ongoing trials aiming to optimize efficacy through monotherapies and synergistic combinations.

3. Emerging molecular targets and predictive strategies in disease therapy

3.1. Txnip: a therapeutic target in type 2 diabetes

Recent advances in molecular medicine have identified a range of novel targets and analytic methods that hold promise for improving therapeutic outcomes in chronic diseases such as type 2 diabetes and cancer. This chapter provides an integrative overview of several such targets, including Txnip and heparanase, and discusses recent developments in antibody-drug conjugates (ADCs) for lung cancer treatment. It concludes with an evaluation of Met-express, an innovative computational framework for metabolic target discovery across cancer types.

Thioredoxin-interacting protein (Txnip) has been increasingly recognized as a critical node in the pathogenesis of type 2 diabetes mellitus (T2DM). It contributes to pancreatic β-cell apoptosis, dysfunction, and insulin resistance. These effects make it a potential therapeutic target for interventions aiming to preserve β-cell function and improve insulin sensitivity. Several commonly used diabetes drugs influence Txnip expression. Verapamil, for example, inhibits calcium signaling and downregulates Txnip, thereby protecting β cells. GLP-1 receptor agonists such as exenatide promote Txnip degradation via the cAMP-ubiquitination pathway, while metformin suppresses its transcription and translation through AMPK activation. These mechanisms collectively support the feasibility of TXNIP-targeted strategies as novel adjuncts in the management of T2DM [6].

3.2. Heparanase: a driver of tumor metastasis

Heparanase plays a pivotal role in cancer metastasis by degrading heparan sulfate proteoglycans (HSPGs), disrupting the extracellular matrix, and releasing angiogenic factors that facilitate tumor progression. Elevated expression of heparanase has been documented in metastatic breast cancer lesions and is positively correlated with recurrence in hepatocellular carcinoma. In cervical cancer, its overexpression promotes disease advancement by inhibiting apoptosis. Functional studies in non-small cell lung cancer (NSCLC) have shown that heparanase knockdown significantly reduces both angiogenesis and invasiveness. These findings underscore its potential as a therapeutic target in the context of metastasis suppression across multiple cancer types.

3.3. Antibody-Drug Conjugates (ADCs) in lung cancer

The development of antibody-drug conjugates (ADCs) has ushered in a new era of targeted therapy in lung cancer. Several promising targets and agents have emerged from recent clinical studies. For HER2-positive NSCLC and breast cancer, trastuzumab deruxtecan (T-DXd) has demonstrated a high

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objective response rate (ORR) of 55%, although it is associated with pulmonary toxicity. HER3-DXd has shown efficacy in cases resistant to EGFR-TKI, with an ORR ranging from 29% to 39%. Trop2-targeting agents such as Dato-DXd have shown effectiveness irrespective of Trop2 expression levels and have produced favorable outcomes when combined with immunotherapy, extending median progression-free survival to 13.1 months. CEACAM5-targeted therapies have achieved ORRs of around 40% in patients with high expression, while c-MET-targeting Teliso-V reached ORRs of over 50% in high-expression subgroups. Rova-T, a DLL3-targeted therapy in small cell lung cancer (SCLC), demonstrated feasibility with an ORR of 14.3%, though hematologic toxicity remains a concern [7].

3.4. Met-express: a dual-network framework for target discovery

In parallel to molecular targeting, computational tools such as Met-express offer a powerful means of discovering therapeutic candidates by integrating gene co-expression data with metabolic network analysis. This platform has enabled systematic investigations across various cancers, including lung, breast, and leukemia. The Met-express approach has led to the identification of 118 key enzyme-encoding genes, encompassing both known and novel drug targets, and 50 metabolic intermediates with potential therapeutic relevance. Notably, three genes and a set of reprogrammed metabolic pathways were consistently implicated across different cancer types. Compared to single-network approaches, Met-express demonstrated significantly improved accuracy and predictive stability. The dual-network integration approach not only enhances the identification of metabolic vulnerabilities in cancer but also offers a scalable paradigm for early-stage drug discovery and biomarker development [8].

Taken together, the molecular targets and analytic frameworks discussed in this chapter represent significant advances in the precision treatment of chronic and oncologic diseases. Continued translational research and clinical validation will be crucial to fully realizing their therapeutic potential.

4. Advances in multi-target strategies for antitumor therapy

4.1. Advantages of multi-target anti-tumor drugs

The emergence of multi-target antitumor drugs represents a pivotal shift in oncology, offering new therapeutic strategies that transcend the limitations of traditional single-target agents. These drugs exhibit three major advantages. First, they exert synergistic effects by simultaneously modulating multiple pathways, which can help overcome drug resistance and broaden therapeutic efficacy. Second, they simplify treatment regimens by reducing the need for combination therapies, thereby lowering the metabolic burden and minimizing adverse drug interactions. Third, their development is compatible with established evaluation systems for small molecule drugs, facilitating clinical translation and regulatory approval [9].

4.2. Dual-target drug NL-101

One illustrative example is NL-101, a dual-target agent that inhibits both histone deacetylases (HDAC3/6) and induces DNA damage. Preclinical studies have demonstrated that NL-101 significantly inhibits the proliferation of multiple myeloma cells both in vitro and in vivo, showing promise as a single agent or in combination with proteasome inhibitors like bortezomib [10].

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4.3. Small molecule multi-target antitumor drugs

Small molecule multi-target antitumor drugs are designed to concurrently target critical oncogenic processes such as angiogenesis (e.g., VEGFR, PDGFR, FGFR), cell proliferation (e.g., EGFR, FLT3), and oncogene signaling (e.g., Raf, c-Kit, RET, MET). Agents such as brigatinib (ALK/ROS1 inhibitor) have shown strong efficacy in ALK-positive NSCLC, while anlotinib and sorafenib are broadly effective in various treatment lines of NSCLC and SCLC, though combination optimization remains essential [3, 11].

4.4. Examples of multi-target drugs

Multitarget drugs exert their effects by engaging diverse intracellular signaling pathways, including PDGFR, RAS/RAF, EGFR, and c-Kit, thereby directly suppressing tumor cell growth. Additionally, by targeting VEGFR signaling, these agents disrupt tumor angiogenesis and modulate the tumor microenvironment. However, their design must balance potency with pharmacokinetic properties, as their typically high molecular weight and lipophilicity often result in reduced oral bioavailability [9].

Monotherapy with multi-target agents such as anlotinib and apatinib has shown survival benefits in advanced NSCLC, whereas sorafenib may be selectively effective in EGFR-mutated populations. Conversely, agents like sunitinib and pazopanib have demonstrated limited efficacy. Combination regimens, particularly in adenocarcinoma with agents such as nintedanib, have yielded partial improvements in PFS, although OS gains remain limited. In SCLC, the challenge persists due to high toxicity and limited biomarker guidance. Thus, molecular subtyping and optimized combination approaches are central to future advancements [12].

Ovarian cancer therapy has also benefited from multi-target strategies. E3 ligase inhibitors like pevonedistat have demonstrated the potential to reverse platinum resistance. Multi-pathway inhibitors targeting VEGF, EGFR, IKKβ, FAK, and CXCR2 have been used to counteract angiogenesis and reduce resistance risk. Immunotherapies such as PD-1/PD-L1 inhibitors offer additional benefit, particularly when guided by biomarker stratification. IL-6/IL-6R blockade using agents like tocilizumab has shown an 85% disease control rate when combined with chemotherapy. Moreover, emerging targets such as macrophage migration inhibitory factor (MIF) are being evaluated for their role in inducing apoptosis in refractory patients. The future of ovarian cancer treatment lies in combining immune modulation, angiogenesis inhibition, and DNA repair targeting with stratified precision medicine based on biomarkers like MIF and PD-L1 [13].

5. Application and prospects

The problem of TNBC metastasis, potential sensitizers in combination with existing therapies, and new strategies for epigenetic regulation [14]. ADC drugs bring breakthroughs to precision treatment of lung cancer, but a balance between efficacy and toxicity is needed, and future focus will be on biomarker screening and combination strategy optimization [15].

The first is the issue of drug resistance. Anti-cancer drug resistance falls into two categories. One is intrinsic resistance: the initial treatment is ineffective due to the absence of a drug target or inherent insensitivity; the other is acquired resistance: a result of adaptive mutations in tumor cells induced by long-term drug use [16].

Next is the issue of social experience and technical support. The evaluation of rare target drugs in our country is still in the exploratory stage, with problems such as the lack of a value framework and

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insufficient attention to social value. The weak chain of evidence for rare tumor target drugs is reflected in the incomplete establishment of specialized databases, the lack of integration of real-world evidence, and the dynamic improvement of efficacy data. There is no innovative assessment method. We should draw on international experience to develop a health outcome evaluation system that suits the characteristics of rare diseases. The multi-subject collaboration is not in place, and a methodological consensus needs to be formed with the joint participation of clinical economic experts and patient representatives in weight design. This approach can consider both scientific and decision-making needs and fully present the value of the drug [17].

Multi-target drugs and combination therapy are currently highly regarded treatment methods, but they still have therapeutic limitations. Compared with combination therapy, multi-target drugs have the advantages of reducing the burden of administration and avoiding drug interactions. The three major challenges they face are, first, insufficient clinical flexibility: it is difficult to rapidly optimize efficacy and safety by adjusting the proportion of components like combination drugs. Second, the molecular design is complex: large molecular weights (often >500) and complex structures break through traditional drug-like rules and require re-establishment of evaluation criteria; Third, mechanistic risks: Target synergy may give rise to novel toxicity, metabolic unpredictability, and dose regulation challenges [11].

Finally, there are inhibitors of targeted drugs. RAF inhibitors target key kinases in the Ras/Raf/MEK/ERK pathway. RAF inhibitors offer an important option for tumor-targeted therapy. Sorafenib has become an important clinical treatment approach and is expected to expand its application range through technological improvements in the future. MEK inhibitors: ATP non-competitive inhibitors that target and block MEK kinase activity and suppress the Ras/Raf/MEK/ERK signaling pathway. MEK inhibitors enhance the efficacy of existing therapies through unique mechanisms of action and show significant potential in overcoming resistance and combination therapy, making them a key complement to targeted therapy [18].

Future research and development could include multi-target drugs, bispecific antibodies, and multi-kinase inhibitors to overcome drug resistance; novel targets such as epigenetics, metabolic pathways (such as IDH1), and undruggable targets (such as KRAS); Combination therapy, immunotherapy + targeting (such as PD-1/EGFR inhibitors); Precise delivery, with reference to nanocarriers and ADC drugs (antibody-drug conjugates) to reduce side effects; In the future, breakthroughs could also be made in AI-designed drugs, PROTAC protein degradation, gene editing (CRISPR), etc.

6. Conclusion

Cancer-targeted therapy has achieved a breakthrough from "indiscriminate killing" to "precise strike" by targeting specific gene mutations, signaling pathways, or tumor microenvironments, significantly improving the efficacy and quality of life of some patients, and expanding its application range in combination with immunotherapy. However, it faces challenges such as drug resistance, target limitations, and tumor heterogeneity. Future research should focus on the discovery of new targets, the resolution of drug resistance mechanisms, the optimization of combination therapy, technological innovations (such as PROTAC, ADC, etc.), and individualized medicine (such as liquid biopsy and organoid models) and promote the development of next-generation targeted drugs through multidisciplinary collaboration, ultimately achieving chronic disease management and precise, humanized treatment of cancer.

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