Journal of Molecular Science

Journal of Molecular Science
Volume 33 Issue 4, Year of Publication 2023, Page 50-52
DoI-17.4687/1000-9035.2023.018

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Targeting Protein-Protein Interactions in Cancer Therapy: Rational Design and Mechanistic Insights into Small-Molecule Inhibitors

George Taylor, Isabella Davies, Jack Wilson, Sophie Thomas

Article Information
Received: 10-11-2023
Revised: 18-11-2023
Accepted: 02-12-2023
Published: 20-12-2023

Keywords
Protein-protein interactions, cancer therapy, small-molecule inhibitors, drug discovery, oncogenic signaling, rational drug design

ABSTRACT
Protein-protein interactions (PPIs) are essential regulators of cellular signaling pathways, and their dysregulation contributes to cancer progression. Targeting PPIs with small-molecule inhibitors (SMIs) has emerged as a promising strategy for cancer therapy. This article explores the structural and functional aspects of PPIs in oncogenic pathways, the principles of rational drug design, and recent advances in small-molecule inhibitors. We discuss computational and experimental approaches to identifying druggable PPIs and review key case studies, such as inhibitors of MDM2–p53, BCL-2 family proteins, and BET bromodomains. Finally, we highlight challenges, current clinical trials, and future directions for PPI-targeted therapies.

1. INTRODUCTION

Cancer is driven by complex signaling networks, many of which rely on protein-protein interactions (PPIs) to regulate cellular processes such as proliferation, apoptosis, and immune evasion. Unlike traditional drug targets, which often involve well-defined active sites in enzymes, PPIs are typically characterized by large, shallow, and dynamic interaction surfaces, making them challenging to target with conventional small molecules. However, recent advances in structural biology, computational modeling, and high-throughput screening have significantly improved the ability to rationally design PPI inhibitors with high specificity and efficacy.

Several innovative strategies have emerged for modulating PPIs in cancer therapy. These include fragment-based drug discovery, stabilized peptide inhibitors, and the development of small molecules that either disrupt critical interaction sites or stabilize inactive protein conformations. Additionally, the advent of proteolysis-targeting chimeras (PROTACs) has revolutionized the field by enabling targeted degradation of oncogenic proteins involved in PPIs.This review provides a comprehensive analysis of current approaches for targeting PPIs in cancer, highlighting recent breakthroughs in drug development, structural insights into key PPIs, and the translational potential

Journal of Molecular Science
Volume 33 Issue 4, Year of Publication 2023, Page 50-52
DoI-17.4687/1000-9035.2023.018

of these therapies. Understanding the mechanisms governing PPIs and overcoming their inherent challenges will be crucial for developing next-generation cancer therapeutics with improved clinical outcomes.

2. Structural Basis of Protein-Protein Interactions in Oncogenic Pathways

2.1 PPI Interfaces and Druggability

PPIs involve extensive contact surfaces, typically composed of hydrophobic and polar residues. Identifying druggable hotspots within these interfaces is crucial for designing effective inhibitors. Table 1 summarizes key oncogenic PPIs and their structural characteristics.

PPI Target	Function in Cancer	Druggability
MDM2–p53	Suppresses p53 tumor suppression	High (deep pocket)
BCL-2–BAX	Prevents apoptosis	Moderate (groove)
BET–Chromatin	Regulates transcription	High (acetyl-lysine recognition)

2.2 Role of PPIs in Cancer Progression

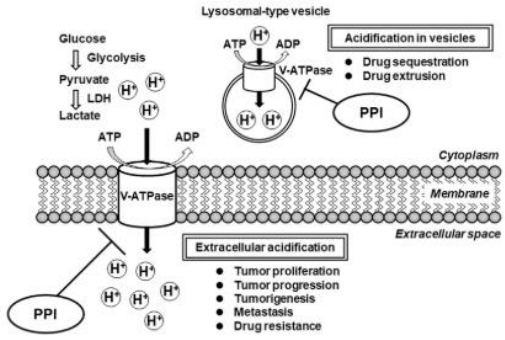

Fig.PPIs in Cancer Progression

PPIs regulate essential cancer pathways such as apoptosis, cell cycle control, and epigenetic modifications. Disrupting oncogenic PPIs restores normal cellular function and promotes tumor cell death.

3. Rational Design of Small-Molecule PPI Inhibitors

3.1 Computational Approaches in Drug Discovery

Molecular docking, molecular dynamics simulations, and AI-driven virtual screening have revolutionized the identification of PPI inhibitors. Structure-based drug design (SBDD) utilizes crystallographic data to identify key binding sites.

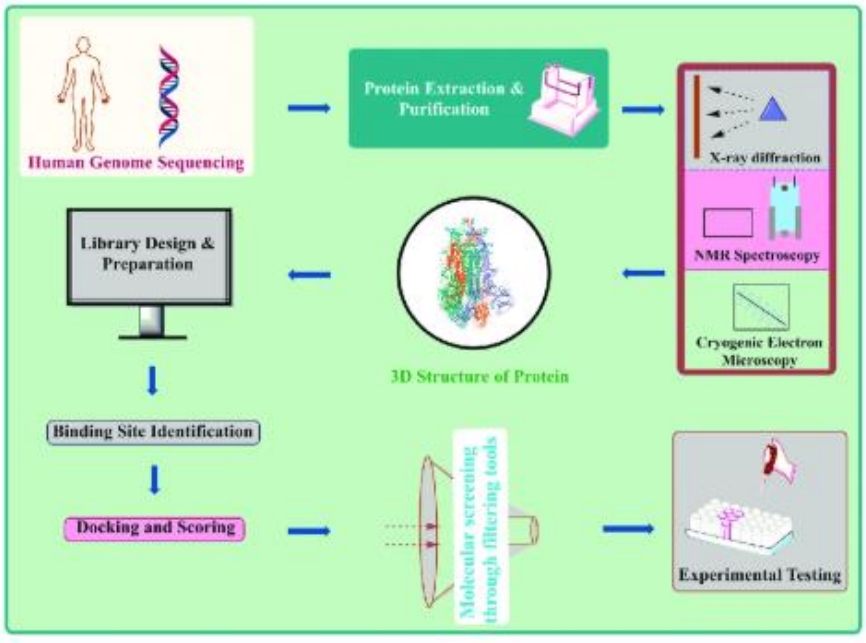

Fig. Structure-based drug design (SBDD)

3.2 Experimental Strategies

Fragment-based drug discovery (FBDD) and high-throughput screening (HTS) have led to the development of lead compounds targeting critical PPIs. Advances in biophysical techniques such as NMR, SPR, and cryo-EM have further refined SMI discovery.

Journal of Molecular Science
Volume 33 Issue 4, Year of Publication 2023, Page 50-52
DoI-17.4687/1000-9035.2023.018

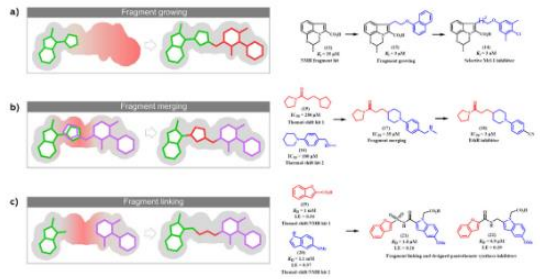

Fig.Fragment-based drug discovery (FBDD)

4. Case Studies: Successful Small-Molecule PPI Inhibitors in Cancer Therapy

4.1 MDM2–p53 Inhibitors

Nutlins and other MDM2 antagonists prevent p53 degradation, restoring tumor-suppressive activity. Clinical trials have demonstrated promising results in hematologic malignancies.

4.2 BCL-2 Family Inhibitors

Venetoclax, a selective BCL-2 inhibitor, induces apoptosis in chronic lymphocytic leukemia (CLL) and has been FDA-approved for treatment.

4.3 BET Bromodomain Inhibitors

JQ1 and OTX015 disrupt BRD4-mediated transcriptional activation, suppressing oncogene expression in hematological cancers.

5. Challenges and Future Perspectives

Despite advances, targeting PPIs remains challenging due to issues with bioavailability, specificity, and resistance mechanisms. Future strategies, including covalent inhibitors, allosteric modulators, and PROTACs, offer novel approaches to overcoming these hurdles.

6. CONCLUSION

Targeting protein-protein interactions (PPIs) with small-molecule inhibitors has emerged as a transformative strategy in cancer therapy, offering new opportunities to disrupt oncogenic signaling pathways that were previously considered undruggable. PPIs play a crucial role in regulating key cellular functions, including proliferation, apoptosis, and immune response, making them attractive therapeutic targets. However, due to their large and often flat interaction surfaces, developing effective inhibitors has posed significant challenges.Recent advances in computational modeling, structural biology, and high-throughput screening have accelerated the discovery of novel PPI inhibitors. Structure-based drug design, fragment-based approaches, and innovative screening techniques have led to the identification of small molecules capable of selectively disrupting PPIs or stabilizing inactive conformations of oncogenic proteins. Additionally, the rise of proteolysis-targeting chimeras (PROTACs) and molecular glues has further expanded the scope of PPI-targeted therapies by enabling selective protein degradation.Despite these advancements, challenges remain, including drug selectivity, bioavailability, and resistance mechanisms. Addressing these limitations will be essential to maximize the clinical impact of PPI-targeted drugs. Future research should focus on optimizing inhibitor specificity, improving drug delivery strategies, and integrating biomarker-driven approaches to enhance patient stratification and treatment efficacy in cancer therapy.

7. REFERENCES

1. Arkin, M. R., & Wells, J. A. (2004). Small-molecule inhibitors of protein-protein interactions: progressing toward the reality. *Nature Reviews Drug Discovery*, **3**(4), 301-317.
2. Vassilev, L. T. (2004). In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. *Science*, **303**(5659), 844-848.
3. Wang, S., et al. (2020). Targeting protein–protein interactions for therapeutic discovery. *Nature Reviews Drug Discovery*, **19**(11), 861-879.
4. Dang, C. V. (2012). MYC on the path to cancer. *Cell*, **149**(1), 22-35.
5. Natarajan, A., et al. (2019). Rational design of small molecules targeting oncogenic PPIs. *Trends in Pharmacological Sciences*, **40**(8), 543-559.
6. Souers, A. J., et al. (2013). Venetoclax: selective inhibition of BCL-2 in CLL. *Nature Medicine*, **19**(2), 202-208.
7. Filippakopoulos, P., et al. (2010). Selective inhibition of BET bromodomains. *Nature*, **468**(7327), 1067-1073.
8. Petros, A. M., et al. (2004). Discovery of a potent BCL-2 inhibitor. *Nature*, **435**(7042), 677-681.
9. Mullard, A. (2021). Protein degraders enter the clinic. *Nature Reviews Drug Discovery*, **20**(3), 247-249.
10. Schreiber, S. L. (2021). The rise of molecular glues. *Cell*, **184**(1), 3-9.
11. Nomura, D. K., et al. (2019). Protein degradation strategies in cancer therapy. *Nature Chemical Biology*, **15**(9), 850-860.
12. Henley, M. J., et al. (2020). Allosteric modulation of protein interactions. *Nature Chemical Biology*, **16**(9), 853-860.
13. Labbé, C. M., et al. (2013). Druggability of protein-protein interactions. *Journal of Medicinal Chemistry*, **56**(7), 2405-2415.
14. Berg, T. (2008). Small-molecule inhibitors of PPIs: challenges and opportunities. *Angewandte Chemie International Edition*, **47**(37), 6476-6480.
15. Dawson, M. A., et al. (2012). Targeting chromatin regulators in cancer therapy. *Nature Reviews Cancer*, **12**(12), 843-856.