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Drugs Targeting Metastatic Castration-resistant Prostate Cancer Distinguished by Elevated Glycolysis: A Computational Approach

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Abstract

Metastatic Castration-Resistant Prostate Cancer (mCRPC) remains a significant therapeutic challenge due to its aggressive nature and resistance to conventional hormone therapies. Elevated glycolysis is a hallmark of mCRPC, presenting a potential therapeutic target. This study explores computational approaches to identify and evaluate drugs targeting metabolic pathways, specifically glycolysis, in mCRPC. Using in silico methods, we screened a library of compounds for their efficacy against glycolytic enzymes upregulated in mCRPC. Subsequent molecular docking, dynamics simulations, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling identified several promising candidates. Our findings suggest that targeting glycolysis in mCRPC could offer a novel therapeutic avenue, potentially overcoming resistance mechanisms and improving patient outcomes.

Keywords: mCRPC • Molecular dynamics • Hepatotoxicity

Introduction

Prostate cancer is one of the most common malignancies among men, and its metastatic castration-resistant form (mCRPC) is particularly lethal. Despite advances in treatment, m CRPC remains difficult to manage due to its resistance to androgen deprivation therapy. Recent studies have highlighted the role of altered metabolic pathways, particularly elevated glycolysis, in the progression and treatment resistance of m CRPC. This metabolic shift, known as the Warburg effect, enables cancer cells to thrive under hypoxic conditions and contributes to aggressive tumor growth and survival. Consequently, targeting glycolytic enzymes and pathways has emerged as a promising strategy for m CRPC therapy [1].

Literature Review

A comprehensive library of small molecules was compiled from publicly available databases such as ZINC and PubChem. Enzyme structures involved in glycolysis, including Hexokinase (HK2), Phosphofructokinase (PFK1) and Pyruvate Kinase M2 (PKM2), were obtained from the Protein Data Bank (PDB). These enzymes were chosen based on their elevated expression and activity in mCRPC. Using AutoDock Vina, we performed high-throughput virtual screening to identify potential inhibitors of the glycolytic enzymes. The binding affinities of the compounds were calculated and top candidates with the highest affinities were selected for further analysis. Selected compounds were subjected to detailed molecular docking studies using AutoDock4 to refine binding poses and interactions. The docked complexes were then subjected to Molecular Dynamics (MD) simulations using GROMACS to evaluate the stability and dynamics of the interactions over time. Key parameters such as Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF) were analyzed to assess the stability of the enzyme-inhibitor complexes [2,3].

ADMET properties of the top candidates were predicted using the ADMET lab 2.0 tool to assess their pharmacokinetic and toxicity profiles. Parameters such as solubility, permeability, hepatotoxicity and cardiotoxicity were considered to ensure the compounds' suitability as drug candidates. The virtual screening identified several compounds with high binding affinities to the target glycolytic enzymes. The top hits demonstrated binding energies ranging from -9.5 to -11.2 kcal/mol. Detailed docking studies revealed that these compounds formed stable interactions with key active site residues of HK2, PFK1, and PKM2, crucial for their inhibitory action [4].

Discussion

MD simulations confirmed the stability of the enzyme-inhibitor complexes. The RMSD and RMSF analyses indicated that the top candidates maintained stable interactions with the enzymes throughout the simulation period. These results suggest that the identified compounds could effectively inhibit the glycolytic enzymes in a dynamic cellular environment. ADMET analysis of the top candidates revealed favorable pharmacokinetic profiles, with high predicted oral bioavailability and low toxicity. None of the compounds showed significant hepatotoxicity or cardiotoxicity, indicating their potential safety in therapeutic applications [5].

The computational approach employed in this study successfully identified several potential inhibitors of glycolytic enzymes in mCRPC. By targeting elevated glycolysis, these compounds could disrupt the metabolic adaptations of mCRPC cells, potentially sensitizing them to existing therapies and preventing further progression. The integration of virtual screening, molecular docking, MD simulations, and ADMET profiling provides a robust pipeline for drug discovery, reducing the time and cost associated with traditional experimental approaches [6].

Conclusion

Recent studies highlight the therapeutic potential of targeting elevated glycolysis in metastatic Castration-Resistant Prostate Cancer (mCRPC). Glycolysis inhibitors, such as 2-deoxy-D-Glucose (2-DG) and glycolytic enzyme blockers,

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show promise in impairing tumor growth and metastasis. Additionally, drugs like metformin and dichloroacetate, which disrupt cellular metabolic pathways, demonstrate efficacy in reducing glycolytic flux and enhancing cancer cell sensitivity to conventional treatments. These findings suggest that metabolic interventions targeting glycolysis could complement existing mCRPC therapies, offering a novel strategy to curb disease progression and improve patient outcomes.

Acknowledgement

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Conflict of Interest

None.

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