Prediction of the penetration efficiency of proapoptotic peptides by cell-penetrating peptides (CPP) and anticancer peptides (ACP) using bioinformatics frameworks

Hajar Pourabtahi[1] and Shahriyar Abdoli[2*]

[1]Department of New Technologies Biotechnology, Golestan University of Medical Sciences,

Gorgan, Iran; hajar.pourabtahi@gmail.com

[2]Assistant professor in Pharmaceutical Biotechnology, Golestan University of Medical Science,

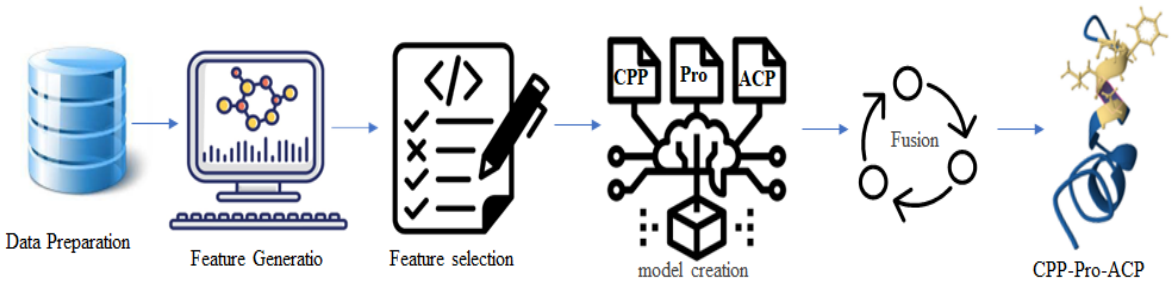
Gorgan, Iran

* Correspondence: drabdoli@goums.ac.ir

Abstract

The use of pro-apoptotic peptides as a potential treatment for cancer is promising, but the hydrophobic barrier of cell membranes poses a challenge. Studies indicate that the use of cell-penetrating peptides (CPPs) can improve intracellular transfer. Our bioinformatics method evaluates four CPPs (TAT, R8, ATP 128, and Penetramax) for transmitting pro-apoptotic sequences (BIM, NOXA, BID, and BMF). Additionally, we incorporated four anti-cancer peptides (LL37, Pexig, CLS001, and Magainin II) to enhance the effectiveness of CPPs. Our method selected 60 CppProAcp sequences with high and medium absorption efficiency and assessed them for various properties, ultimately identifying 20 promising structures. This workflow can be applied to any CPP-peptide conjugation scheme.

Key Word: pro-apoptotic peptides, cell-penetrating peptides, anti-cancer peptides, Delivery, CPP-peptide



Introduction

BH3 mimetics are promising for cancer treatment, but challenges like low uptake and lack of selectivity exist. Scientists are working to improve their effectiveness. Penetrating peptides can carry drugs and enter cells. There are 1855 types recorded in the CPPsite 2.0 database. They can be derived from natural or non-natural proteins and transport various cargo types. CPPs can deliver proapoptotic peptides for cancer treatment.ACP peptides, combined with CPPs, have potential in oncology treatment. CppProAcp, a non-toxic and non-antigenic compound, shows promise for clinical application. Our SkipCPP-Pre model uses machine learning to predict CppProAcp activity, aiding targeted cancer treatment development.

Results and Discussions:

We analyzed 12 peptide sequences for cellular uptake and stability and found 60 with high or moderate uptake efficiency. Most peptides had basic pI and a high aliphatic index, and stable peptides had an instability index below 40. CPP sequences did not significantly affect solubility. We found that proapoptotic and antimicrobial peptides can affect structure, but CPP sequences do not contribute. The folding rate is important for proper function, and CppProAcp sequences require a very low folding rate. None of the 32 selected sequences were found to be toxic.

Materials and Methods

We obtained CPP and ACP sequences from databases and predicted their absorption efficiency using CPPred-RF. Physiochemical properties, solubility, and 3D structures were analyzed using online tools such as ProtParam, RCSB PDB, and SCOOP/FoldX. We also analyzed the potential for allergies, immunogenicity, RBC lysis, and toxicity using web servers like AllergenFP, VaxiJen V2.0, HemoPI, and ToxinPred

Conclusion

Our research focused on the obstacles in delivering pro-apoptotic peptides as anticancer drugs, and recent developments in tumor targeting. We retrieved CPP and ACP sequences from databases and used CPPred-RF to predict their absorption efficiency for proapoptotic transfer. Our study provides a foundation for further investigations in vitro and in vivo and offers an opportunity to integrate independent peptides as a potential source for biotherapeutics or drug carriers.

Reference

1-Nasiri F, Atanaki FF, Behrouzi S, Kavousi K, Bagheri M. CpACpP: in silico cell-penetrating anticancer peptide prediction using a novel bioinformatics framework. ACS omega. 2021;6(30):19846-59.

2-Behzadipour Y, Hemmati S. Considerations on the rational design of covalently conjugated cell-penetrating peptides (CPPs) for intracellular delivery of proteins: a guide to CPP selection using glucarpidase as the model cargo molecule. Molecules. 2019;24(23):4318.

3- Singh V, Khurana A, Navik U, Allawadhi P, Bharani KK, Weiskirchen R. Apoptosis and pharmacological therapies for targeting thereof for cancer therapeutics. Sci. 2022;4(2):15.