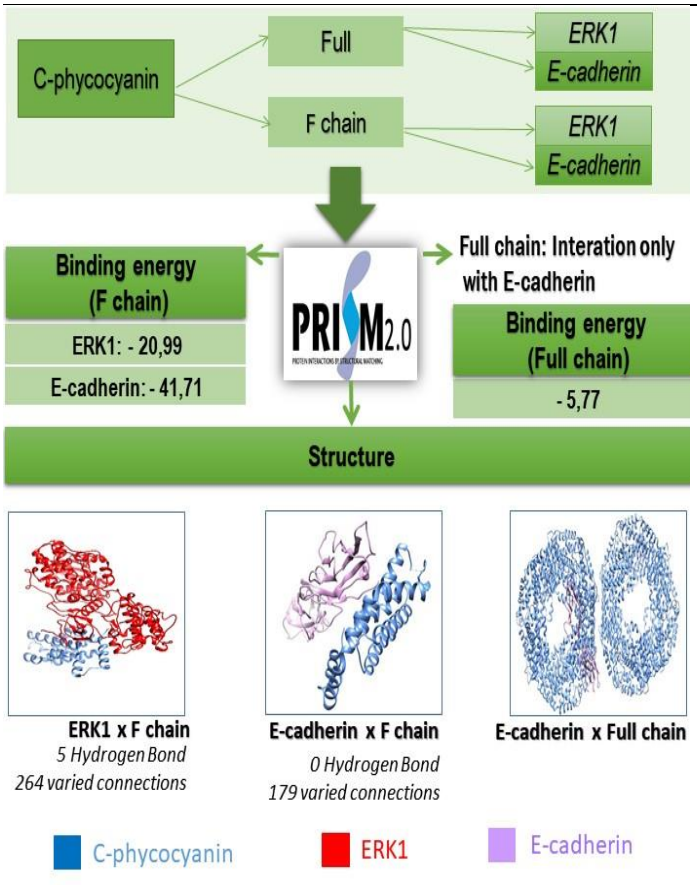
MOL2NET, International Conference Series on Multidisciplinary Sciences
CHEMINFOUNC-02: Chemoinformatics Workshop, UNC Chape Hill, USA, 2020

In silico protein-protein interaction: C-phycocyanin has potential for block proliferation and adhesion proteins in cancer

Estela Fernandes e Silva[a]; Paula Fernandes e Silva[b]; Juliana Silva Lemões [c]; Mariana T.S. F. Salgado[d]; Ana Paula de Souza Votto[d]; Tainã F. Cardoso[e]; Timóteo Matthies Rico[*]*

*a Doctor in Physiological Sciences by Universidade Federal do Rio Grande - FURG, Rio Grande (Rio Grande do Sul), Brasil; *e-mail address: star.fs@hotmail.com*
b Dentist by Universidade Federal de Pelotas, Pelotas (Rio Grande do Sul), Brasil
c Doctor in Chemistry by Universidade Federal do Rio Grande do Sul, Professor at Universidade Federal do Pampa, Bagé (Rio Grande do Sul), Brasil
d Programa de Pós-Graduação em Ciências Fisiológicas, Universidade Federal do Rio Grande - FURG, Rio Grande (Rio Grande do Sul), Brasil
e Postdoc at Embrapa Pecuária Sudeste, São Carlos, Brazil
f Doctor in Health Sciences by Universidade Federal do Rio Grande - FURG, Professor at Instituto-Federal-Sul-Riograndense, Jaguarão (Rio Grande do Sul), Brasil



Abstract. *The pathophysiology of cancer is related to diverse cellular and molecular dysfunctions. Unregulated proliferation can occur due to changes in pathways such as MAP kinase (ERK is the effector kinase). Metastasis linked to the worst prognosis is related to the unregulated function of adhesion proteins (like E-cadherins/ ECAD). The C-phycocyanin (C-PC) is a photosynthetic pigment with several biological activities, with the potential to inhibit ERK and ECAD in tumors. In this work, we evaluated the possible interaction of C-PC with ERK1 and ECAD to deepen the knowledge about the anti-tumor mechanisms of C-PC. Using the PRISM web server (algorithm based on structural matching) the interaction of the C-PC was verified (PDB ID: 1GH0) in its complete form (Full) or F chain with ERK1 (PDB ID: 2ZOQ) and ECAD (PDB ID: 2O72). Full C-PC interacted with ECAD with -5.77 of binding energy (BE). The F chain interacted with ERK1 (-20.99 BE) and ECAD (-41.71 BE). UCSF Chimera program revealed that the F chain*

	binding to ECAD by 179 varied connections (polar, nonpolar, favorable and unfavorable), without establishing Hydrogen bonds. The chain F binding to ERK1 by 5 Hydrogen bonds and 264 varied connections. The chain F of C- seems to have greater biological action (in relation to the complete structure), because it was linked to the two targets. The greater BE demonstrates the greater stability of the protein complex, so the greatest action must occur on ECAD. However, the interaction in ERK1 by 5 hydrogen bonds should favor the role of C-PC on this protein. Thus, the interaction of C-PC with ERK1 and ECAD demonstrates its potential to reduce proliferation and metastasis, encouraging in vitro studies.

Introduction

. *There are several cellular dysfunctions that support the pathophysiology of cancer. The Mitogen-Activated Protein Kinase (MAPK) pathway (also known as the RAS-RAF-MEK-ERK pathway, being ERK the effector kinase), which controls of cellular growth, survival, and differentiation can presents aberrant activation in many human cancers* (1). *Another important example is the E-cadherins. E-cadherin (ECAD) is a key component of the adherens junctions that are integral in cell adhesion and its loss results in loss of contact inhibition and is associated with advanced stages of cancer* (2). *Thus, molecules that act on ERK e ECAD would be excellent agents in chemotherapy. In this context, the C-phycocyanin (C-PC), a photosynthetic pigment with several biological activities* (3), *has potential to inhibit ERK and ECAD in tumors, because it has already demonstrated several anti-tumor properties. Therefore, the objective of this study was to evaluate the possible interaction (through molecular docking) of C-PC with ERK and ECAD to deepen the knowledge about the anti-tumor mechanisms of C-PC.*

Materials and Methods

Proteins structures were obtained from Protein Data Bank (PDB) (4) *according PDB ID. For protein interaction verification we used the PRISM web server, (available on http://cosbi.ku.edu.tr/prism/) considering C-PC (PDB ID: 1GH0, in full structure or F chain only), human mitogen-activated kinase ERK1 (PDB ID 2ZOQ) and human E-cadherin (PDB ID 2O72). Each target was subjected to docking simulation with: 1- C-PC full structure and 2- only F chain totaling 4 docking simulations (we provided on the server PDB ID for each pair of proteins). The possible binding modes were generated by server (number of possible binding modes depending of pair analyzed) and only the most negative binding energy (greater stability) was showed in results. The binding mode with greater binding energy was analyzed with UCSF Chimera program (available to download at http://www.cgl.ucsf.edu/chimera/download.html).for verification of Hydrogen bonds and varied connections (polar, nonpolar, favorable and unfavorable) established between molecules.*

Results and Discussion

Only ECAD obtained docking with the complete structure of the C-PC (Full) (Fig. 1A), with binding energy (BE) of -5.77. On the other hand, the F chain interacted with ECAD (-41.71 BE) (Fig. 1B) and ERK (-20.99 BE) (Fig. 1D). A more negative BE indicates greater affinity and stability of the protein complex (5,6), *thus the F chain seems to be the one with the greatest biological action, and*

ECAD seems to be the preferred target of C-PC. However, a more detailed analysis of the binding pattern showed that F chain binding to ECAD by 179 varied connections (polar, nonpolar, favorable and unfavorable) (Fig. 1C), without establishing Hydrogen bonds. Already the binding of F chain to ERK1 established 5 Hydrogen bonds (Hbonds) (Fig. 1E) and Hbonds are a type of bond that strongly influences the biological activity of molecules (7)*. Besides that, the F chain established to ERK1 more varied connections (264 connections) (Fig. 1F) in relation to ECAD. Taking together the binding energy and the types of binding established between the molecules, it appears that both ECAD and ERK1 are excellent targets for C-PC in a possible therapy.*

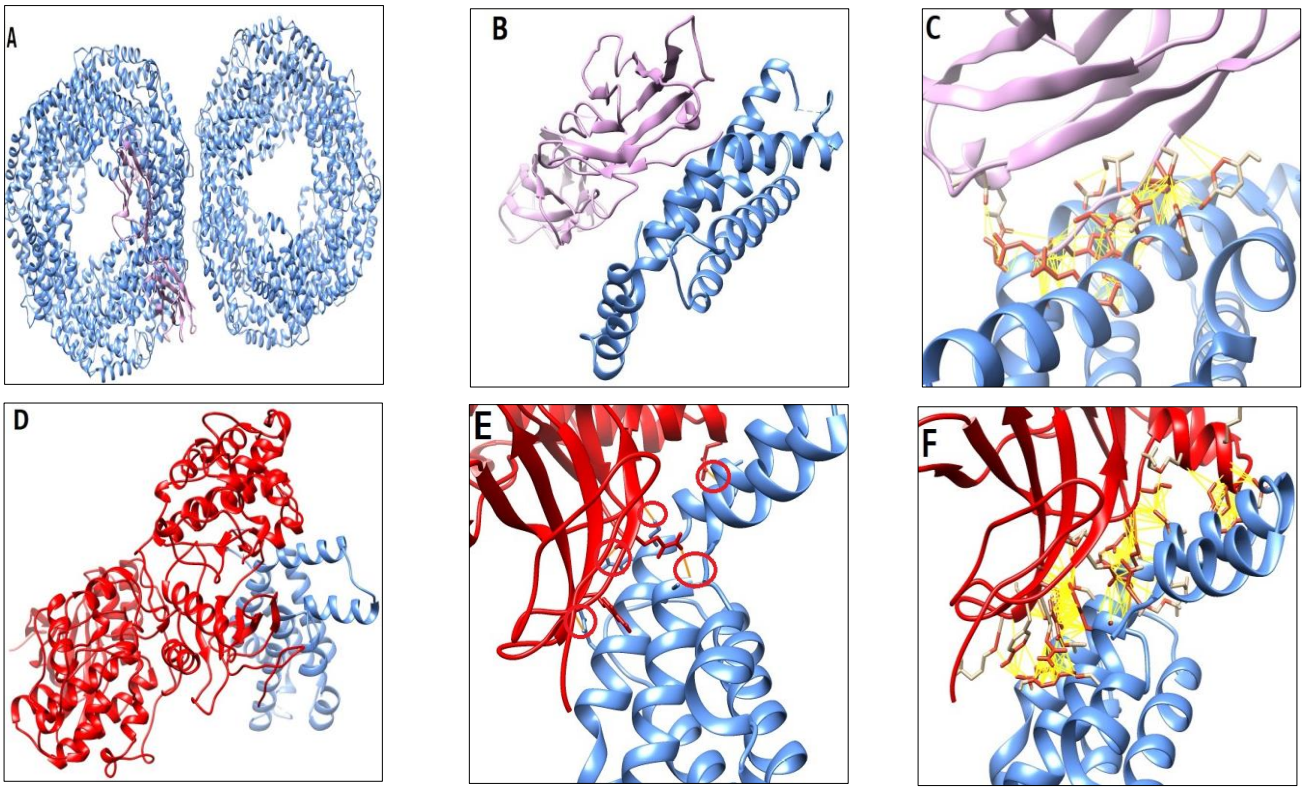


Figure 1: C-phycocyanin (C-PC in blue); E-Cadherin/ECAD (violet); ERK1 (red). ECAD-Full C-PC complex (A); ECAD-F chain complex (B); varied connections (polar, nonpolar, favorable and unfavorable/ yellow lines) of ECAD- F chain complex (C); ERK1-F chain complex (D); Hydrogen bonds (orange lines with red circle aroud) of ERK1-F chain complex (E); varied connections (polar, nonpolar, favorable and unfavorable/ yellow lines) of ERK1-F chain complex (F).

Conclusions

The interaction of C-PC with ERK and ECAD demonstrates its potential to reduce proliferation and metastasis on cancer, encouraging in vitro and in vivo studies.

References

1. Masliah-Planchon J, Garinet S, Pasmant E. RAS-MAPK pathway epigenetic activation in cancer: MiRNAs in action. Oncotarget. 2016;
2. Mendonsa AM, Na TY, Gumbiner BM. E-cadherin in contact inhibition and cancer. Oncogene. 2018.
3. Fernandes e Silva E, Figueira FS, Cañedo AD, Machado KS, Salgado MTSF, Silva TK, et al. C-phycocyanin to overcome the multidrug resistance phenotype in human erythroleukemias with or without interaction with ABC transporters. Biomed Pharmacother. 2018;
4. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The Protein Data Bank (www.rcsb.org). Nucleic Acids Res. 2000;
5. Tuncbag N, Gursoy A, Nussinov R, Keskin O. Predicting protein-protein interactions on a

proteome scale by matching evolutionary and structural similarities at interfaces using PRISM. Nat Protoc. 2011;

6. Baspinar A, Cukuroglu E, Nussinov R, Keskin O, Gursoy A. PRISM: A web server and repository for prediction of protein-protein interactions and modeling their 3D complexes. Nucleic Acids Res. 2014;
7. Sigala PA, Ruben EA, Liu CW, Piccoli PMB, Hohenstein EG, Martínez TJ, et al. Determination of hydrogen bond structure in water versus aprotic environments to test the relationship between length and stability. J Am Chem Soc. 2015;

.
.
.