Structural elucidation of proline-based inhibitors against enabled/vasodilator stimulated phosphoprotein to control metastasis

Arunkumar Kalla, Insha F. Shaik, Bindu S. Nallamilli and Ravikiran S. Yedidi*

The Center for Advanced-Applied Biological Sciences & Entrepreneurship (TCABS-E), Visakhapatnam, Andhra Pradesh, India. 530002.

*Correspondence to RSY: tcabse.india@gmail.com

INTRODUCTION

Cancer is a group of diseases involving abnormal cell growth which spread to other parts of the body. There are more than 100 types of cancers such as metastatic breast cancer,lung cancer etc. Metastatic breast cancer may spread to any part of the body. It most often spread to the bones,liver,lungs and brain. Mutations in DNA can cause normal breast cancer.Mutated DNA can lead to mutated genes. Proto-oncogenes are genes that help cells normally, when these genes mutate or too many copies are produced then this leads to cancer.

The spread of cancer cells from the place where they first formed to another part of the body is metastasis. For example, if breast cancer spreads to the lungs the cancer cells in the lungs are breast cancer cells , not lung cancer cells.Some of the treatments for breast cancer are radiation therapy, surgery, chemotherapy and targeted therapy.Cancer is leading cause of death worldwide, about 276,480 new cases of invasive breast cancer will be diagnosed in women & 48,530 new cases of carcinoma insitu will be diagnosed. About 42,170 women will die from breast cancer.

Vasodilator –stimulated phosphoprotein (VASP) is associated with filamentous actin formation and plays a widespread role in cell adhesion and motility. VASP may also be involved in the intracellular signaling pathways that regulate integrin-extracellular matrix interaction. VASP is regulated by the cyclic nucleotide- dependent kinase PKA & PKG. The three vertebrate Ena/VASP family members, share a tripartite structural organization in which EVH1 & EVH2 (homology domains) are separated by a more divergent proline-rich central part. Ena/VASP proteins are discussed as a part of the invasive signature and as a marker of breast carcinogenBattling metastasis through inhibition of cell motility is considered a promising approach to support cancer therapies. Ena/VASP-depending signaling pathways, in particular interactions with their EVH1 domains, are promising targets for pharmaceutical intervention. However, protein-protein interactions involving proline-rich segments are notoriously difficult to address by small molecules. Hence, structure-based design efforts in combination with the chemical synthesis of additional molecular entities are required.

EXPERIMENTALS

In order to understand the overall structure of VASP in breast cancer ,3- dimensional analysis of the structure was performed using computational biology tools. Structure of VASP was downloaded from the protein data bank (PDB ID:7A5M). The analysis includes secondary structure (alpha helix & beta strands) followed by hydrogen bond analysis using pymol software. A small molecule binding sites are identified.

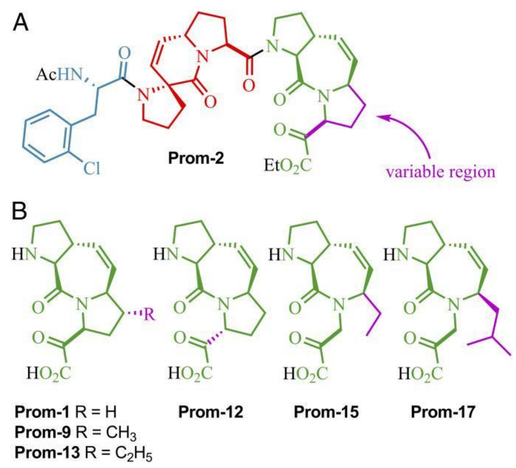
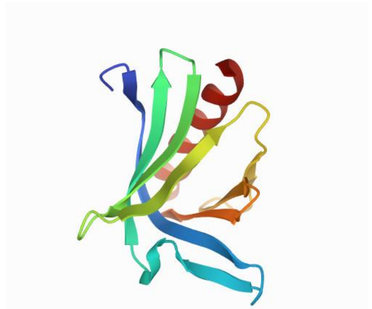
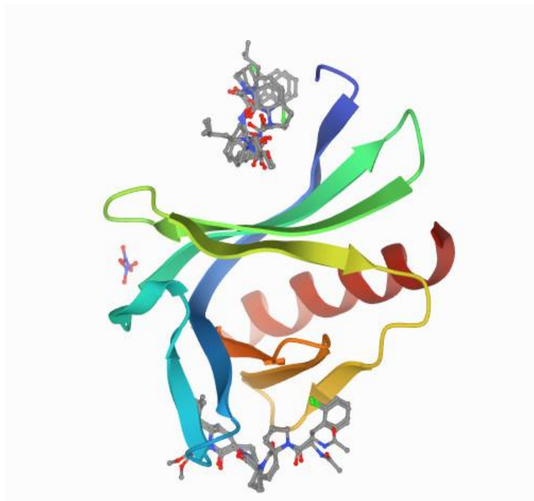


Fig. 1. (*A*) Structure of the first-generation Ena/VASP EVH1 inhibitor **1**. All compositions share the *N*-acetylated 2-chloro-phenylalanine unit (blue) attached to a central ProM-2 scaffold (red). Esterification of the C terminus renders the inhibitors cell-membrane permeable (40). (*B*) General (modular) architecture of nonpeptidic, conformationally preorganized inhibitors used in this study. Structural variation (pink) was achieved by replacing the C-terminal ProM-1 unit (green) by ProM-9, ProM-13, ProM-12, ProM-15, or ProM-17 (Table 1).



Protein enabled homolog



7A5M STRUCTURE

RESULTS & DISCUSSION

The structure of VASP (PDB ID: 7A5M) contains one chain that contain 2 alpha helix and 8 beta strands.It contains 2 macromolecule which are - Protein enabled homolog and Ac-[2-Cl-F]-[ProM-2]-[ProM-17]-OMe Followed by structural analysis, NO3 Is one of the ligand

This study represents an example of successful, structure-guided development of low molecular weight inhibitors specifically and selectively addressing a proline-rich sequence-recognizing domain that is characterized by a shallow epitope lacking defined binding pockets.

REFERENCES

1.A modular toolkit to inhibit proline-rich motif-mediated protein-protein interactions. Opitz, R., Muller, M., Reuter, C., Barone, M., Soicke, A., Roske, Y., Piotukh, K., Huy, P., Beerbaum, M., Wiesner, B., Beyermann, M., Schmieder, P., Freund, C., Volkmer, R., Oschkinat, H., Schmalz, H.G., Kuhne, R. (2015) Proc Natl Acad Sci U S A **112: 5011**

2. *"Breast Cancer Treatment (PDQ®)". NCI. 23 May 2014. Archivedfrom the original on 5 July 2014. Retrieved 29 June 2014.- wikipedia*

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