The Significance of Beta-Turns in Finding a Breast-Cancer Inhibiting, Non-Peptide Mimetic

Katherine Alser '09, Katrina Lexa '05, Amanda Salisburg '08, Karl Kirschner, George Shields
Department of Chemistry, Hamilton College, Clinton NY 13323
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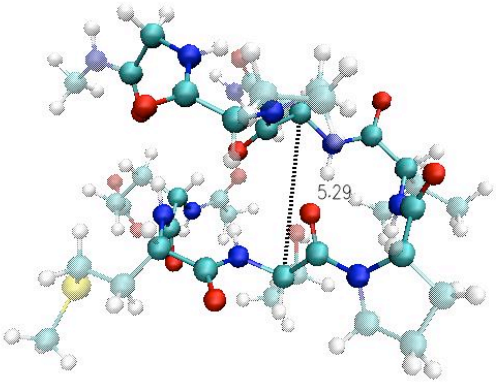
Alpha-fetoprotein, AFP, is found in the blood or amniotic fluid of pregnant women. Though the function of AFP in relation to a fetus is not well understood,[1] segments of the protein between four and nine amino acids in size inhibit the growth of estrogen-dependent breast cancer cells[2]. The goal of our research is to determine which behavior and structure aspects result in the most effective breast-cancer inhibition. Once this is understood we can design a non-peptide mimetic to be used as a potential drug to treat breast cancer.

The inhibition of cancerous cell growth is a result of the antagonistic binding of a beta-turn conformation of a peptide to the DNA of the cancer cells. A beta-turn consists of four consecutive amino acids[3], which will be referred to as amino acids one, two, three, and four. We can determine what type of beta turn a particular peptide adopts via the analysis of Ramachandran plots, or plots of the phi vs. psi angles of amino acids two and three over an entire simulation. In addition to the traditional definitions, a beta-turn is also defined as any conformation in which the distance between the alpha-carbon belonging to amino acid one and the alpha-carbon belonging to amino acid four is less than 7.00 Angstroms.[4] We were able to determine how often a particular peptide adopts a beta-turn conformation using Amber's ptraj program to find the distances between these two alpha-carbons over a simulation. The figure below is a snapshot of beta-turn within an active octapeptide during a time step in the simulation at which the distance between the two significant alpha-carbons is 5.29 angstroms. Our analysis showed that all of these AFP peptide derivatives assume a beta-turn conformation from 60% to100% of the time. The peptides that assume a beta-turn conformation for higher percentages of the time are generally more active in the inhibition of breast cancer cell growth. To further analyze what elements of dominantly active structures contribute to the formation of a beta-turn conformation, we decided to look into intra-molecular hydrogen bonding of the peptides. From our analysis of the peptides, we hope to identify a dominant active structure, and which aspects of the structure contribute to the inhibition of breast cancer cell growth.



Octapeptide EMTPVNPG

[1] TC-Cancer.Com. 17 July 2006. 17 July 2006 <http://www.tc-cancer.com/dictionary.html>.
[2] Kirschner, Karl N., Katrina W. Lexa, Amanda M. Salisburg, Katherine A. Alser, Leroy Joseph, Thomas T. Andersen, James A. Bennett, Herbert I. Jacobson, and George C. Shields. "Computational Design and Discovery of an Anti-Estrogenic Peptide Derived From Alpha-Fetoprotein." Nature (2006).
[3] Hutchinson, Gail. "Beta Turns." BSM Group. 22 May 1996. UCL Department of Biochemistry and Biology. 7 July 2006 <http://www.biochem.ucl.ac.uk/bsm/promotif/betaturns.html>.
[4] Kaur, H. and Raghava, G.P.S. (2002) BetaTpred:Prediction of beta-turns in a protein using statistical algorithms. Bioinformatics 18:498-9