Identification and computational evaluation of possible allosteric and competitive inhibitors of human PEPCK-M: an alternative therapy for lung carcinoma

Luiz Phillippe Ribeiro Baptisa[1], Vanessa de Vasconcelos Sinatti Castilho[1], Ana Carolina Ramos Guimarães[1]

1 FIOCRUZ-IOC

Abstract

Cancer is the second largest cause of death in the world, posing a huge problem for modern medicine. The increase in the number of cells, the result of uncontrolled cell division, leads to an increasing requirement of glucose consumption. Tumor growth under conditions of metabolic limitation, especially with decreased glucose availability, is common, suggesting that tumor cells exhibit high metabolic plasticity. Central to this adaptation, there is the enzyme phosphoenolpyruvate carboxykinase (PEPCK) that participates in the initial phase of gluconeogenesis. This enzyme acts on the reversible formation of phosphoenolpyruvate (PEP) from oxaloacetate (OAA). Due to its gluconeogenic function, the differential expression of cytoplasmic (PEPCK-C) and mitochondrial isoforms (PEPCK-M) is independently associated with different types of cancer. Recent studies have shown that this change is critical in lung cancer, in which tumor cells submitted to low glucose levels increase the expression of PEPCK-M. Also, inhibition or the knockdown of the PEPCK-M enzyme in lung tumor cell cultures led to increased cell death and apoptosis. These studies show the importance of this enzyme to the prevalence of cancer. In this work, we intend to explore the enzyme PEPCK-M as a target for a computer-aided drug design that can be used in the therapy of lung cancer. Although very important, there are no 3D structures deposited in the PDB for PEPCK-M (unlike its isoform, PEPCK-C). For this reason, we performed a comparative modeling using the program MODELLER. Comparative analyses between the two isoforms have shown that they are very similar - presenting high conservation between active and allosteric site residues. The electrostatic potential analysis, performed with APBS, also indicated strong similarities - both enzymes have an overall electropositive active-site cleft. We also conducted redocking experiments with Glide XP and Autodock Vina to test which program is the most suitable for future experiments. The observation of mutations commonly found in lung cancers was another important analysis. This experiment used the mutation database COSMIC. The most frequent mutations were mapped on the PEPCK-M structure. These results suggest that the PEPCK-M enzyme has structural characteristics like those shown in PEPCK-C - validating the use of inhibitors described for the cytoplasmic enzyme. Also, the localization of common mutations in lung cancer, both in the catalytic cleft and allosteric site, favor the search for specific inhibitors for the mutated PEPCK-M.

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