ANTIPROLIFERATIVE OXIME DERIVATIVES THAT INHIBIT GLUCOSE TRANSPORTER 1 (GLUT1) IN CANCER CELLS

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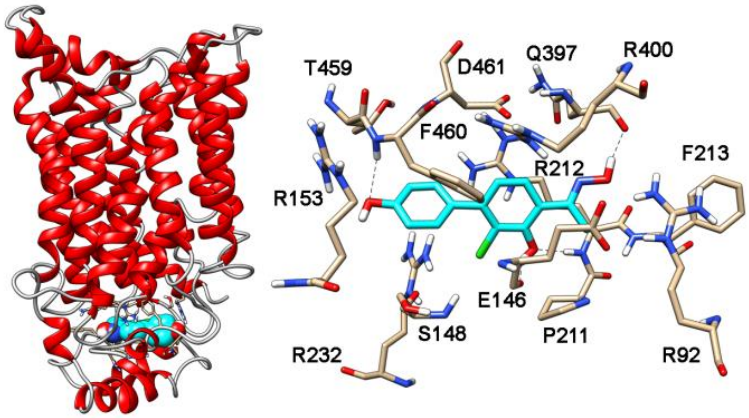
Abstract

The Warburg effect, consisting in alterations of the glucose metabolism in cancer cells, where glucose mostly undergoes glycolysis with production of lactate, is currently being considered as one of the most intriguing hallmarks of cancer.[1] Therefore, the discovery of new agents able to block the glycolytic processes in tumor cells holds promise for developing relatively nontoxic anticancer treatments.[2]

In terms of energy (ATP) production, glycolysis is dramatically less efficient than oxidative phosphorylation (OXPHOS). In fact, most normal cells rely on OXPHOS for glucose degradation, since they are generally well-oxygenated. On the contrary, invasive tumor tissues are often exposed to more-or-less transient hypoxia, which cannot guarantee the proper functioning of OXPHOS. Under these hypoxic conditions glycolysis leading to lactate production is mainly preferred, since it does not depend on oxygen availability. However, due to the lower efficiency of the glycolytic process, cancer cells commonly show a remarkably high glucose uptake, which is supported by the overexpression of the glucose transporters (GLUTs). GLUT1 is one of the most commonly transporters that are overexpressed by cancer cells and, therefore, represent a potential target for selectively hitting them,[3] although only a very limited number of GLUT1-inhibitors have been reported so far.[4]



On the basis of an analysis of the pharmacophoric features displayed by some previously reported GLUT1-inhibitors, we have identified a series of oxime derivatives[5] as potentially active on this transporter. A preliminary screening of these compounds in H1299 lung cancer cells demonstrated that some of them are able to effectively counteract glucose uptake and cell growth, displaying IC_{50} values in the low micromolar range. We have then developed a new computational model of GLUT1, which provided us with valuable clues about the possible binding site and the most important interactions occurring with some representative oxime derivatives and GLUT1. These indications may prove to be very valuable for the future development of novel potent and selective GLUT1-inhibitors.

References:

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