Poster Presentation

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Malic enzyme is a target for drug design to combat obesity and cancer

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The cytosolic malic enzyme (ME1) plays an important role in insulin-induced lipogenesis and has profound effects on colon cancer progression. ME1 generates pyruvate, NADPH and carbon dioxide from malate, a Krebs cycle intermediate. NADPH has an important role in de novo synthesis of long-chain fatty acids whereas pyruvate is cycled back into mitochondria. The pyruvate cycle has been hypothesized to be a necessary component of glucose-stimulated insulin secretion. Increased insulin signaling in liver and adipose tissues leads to higher accumulation of fat mass increasing the risk for obesity. NADPH and fatty acids also support cancer cell proliferation and migration. Thus ME1 may be a suitable drug target to counter obesity and prevent cancer progression. In the current work, computer-aided drug design techniques were used to identify possible ME1 inhibitors with therapeutic value. The software package SYBYL was used for defining the binding pocket and virtual screening was performed to mine through large databases (ZINC-UCSF) containing drug-like molecules in order to identify molecules that could form hydrogen bonds to the enzyme and fit into the active site. The molecules so obtained were then used for docking using the software packages SURFLEX DOCK (SYBYL) and AutoDock Vina (Scripps Research Institute). Lead molecules having minimum binding energy score were identified and two in vitro assays were carried out on the top hit molecules. We tested a total of 11 compounds for activity using an enzyme assay and 4 of these compounds were found to diminish NADPH production significantly. Additionally we performed a cell proliferation assay with colorectal cancer cell line (HCT-116) using the above 4 compounds and three of these compounds exhibited strong activity against cancer cell growth. Supported in part by NIH grant CA136493.

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