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Extended Abstract

Dibenzylxanthines as PPEPCK-M Inhibitors for Cancer Therapy †

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Phosphoenolpyruvate carboxykinase (PEPCK) is the key enzyme in gluconeogenesis/glyceroneogenesis, which catalyzes the decarboxylation of oxaloacetate to phosphoenolpyruvate. In eukaryotes, there are two isozymes present either in the cytosol (PEPCK-C, PCK1) or the mitochondria (PEPCK-M, PCK2). While PCK1 is found in gluconeogenic tissues and has a very clear metabolic function, PCK2 is expressed in non-gluconeogenic cell types, where its role remains largely unknown. For example, PCK2 is highly expressed in most cancer cells, where it provides a growth advantage to cancer cells in nutrient-poor environments.

A group of C-8 modified 3-alkyl-1,8-dibenzylxanthine derivatives was described as a novel PEPCK-C inhibitor family. We hypothesized that this family of inhibitors could cross-inhibit both PEPCK-C and PEPCK-M due to their nearly identical active center. To determine the validity of our claim, we studied PEPCK-M target engagement using INH2—the most potent compound of the family—and showed similar quantitate inhibitory kinetics to PEPCK-C. Therefore, we validated PEPCK-M as a cancer target using INH2 and compared its efficacy to 3-mercaptopicolinic acid, a classical, low potency PEPCK-C inhibitor.

Treatment of colon and breast carcinoma cell lines with INH2 was shown to inhibit cell proliferation, and it decreased cell survival in poor-nutrient environments. Inhibition of PEPCK-M with INH2 also reduced colony formation in a soft agar model of anchorage-independent growth. Finally, we tested the inhibitor in two subcutaneous xenograft models—SW-480 colon carcinoma and MDA-MB-231 breast carcinoma. Daily dosing with 8.3 mg/kg of INH2 successfully inhibited tumor growth with respect to the vehicle treatment group. There was no weight loss or any sign of apparent toxicity induced by the treatment.

Our results suggest that PEPCK-M is a valid target for cancer treatment with specific inhibitors.