Introduction

A. PDH E1 complex altered in cancer cell metabolism. Note the blocked sulfurs. (Figures 1A and B)

B. Peroxiredoxins are a class of cellular antioxidants that exist in both mitochondrial (Prx-III) and cytosolic (Prx-I) forms. Treatment with active glutaredoxin scavenged by antioxidants (NAC, Tiron). B. Peroxiredoxins are a class of cellular antioxidants that exist in both mitochondrial (Prx-III) and cytosolic (Prx-I) forms. Treatment with active glutaredoxin scavenged by antioxidants (NAC, Tiron).

Thioctoids Results

A. In vitro Glutathionylation of KGDH inhibits Activity

B. Reduced redox status in a time- and dose-dependent manner. Thioctoids inhibit PDH and KGDH activity as assessed (see Figure 5).

C. Schematic of the reaction quantified in (A). Carbons 3 & 4 of glucose become C-1 of pyruvate after glycolysis and are released as CO2 after decarboxylation by PDH. C-1 of glutamate is released after decarboxylation by PDH. C-1 of glutamate is released after decarboxylation by PDH. C-1 of glutamate is released after decarboxylation by PDH.

Results

A. Thioctoids inhibit PDH activity as measured by reduction in 3,4-[14C]glucose oxidation.

B. Thioctoids inhibit KGDH activity as measured by reduction in 1-14C glutamic acid oxidation.

Conclusions

Tumor cell metabolism is emerging as a promising chemotherapeutic target. We have previously shown that thioctoids inhibit PDH via phosphorylation[2]. Here we demonstrate an additional inhibitory effect on the Krebs cycle enzyme KGDH via a ROS-dependent glutathionylation mechanism. Thioctoids appear to target multiple lipoate-containing mitochondrial enzymes and may in fact act as a ‘cocktail-of-one,’ perturbing tumor cell metabolism at multiple sites. These drugs are currently in human clinical trials and our pre-clinical studies indicate that they may have unique promise.

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References