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(54) Title: TARGETING METABOLIC ENZYMES IN HUMAN CANCER

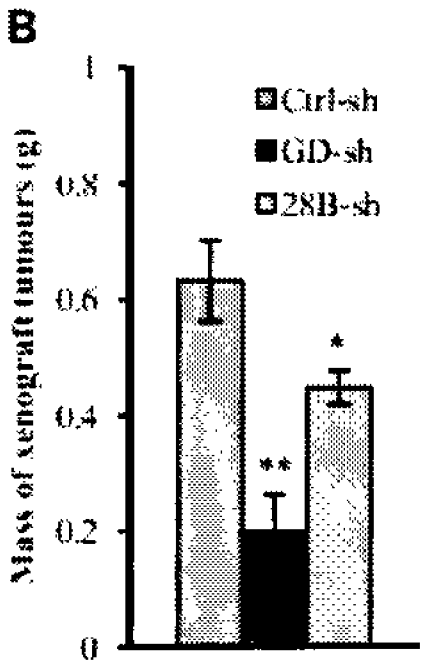


Figure 10

(57) Abstract: Targeting metabolic enzymes in human cancer Abstract Lung cancer is a devastating disease and a major therapeutic burden with poor prognosis. The functional heterogeneity of lung cancer (different tumor formation ability in bulk of tumor) is highly related with clinical chemoresistance and relapse. Here we find that, glycine dehydrogenase (GLDC), one of the metabolic enzyme involved in glycine metabolism, is overexpressed in various subtypes of human lung cancer and possibly several other types of cancers. GLDC was found to be highly expressed in tumor-initiating subpopulation of human lung cancer cells compared with non-tumorigenic subpopulation. By array studies we showed that normal lung cells express low levels of GLDC compared to xenograft and primary tumor. Functional studies showed that RNAi inhibition of GLDC inhibits significantly the clonal growth of tumor-initiating cells in vitro and tumor formation in immunodeficient mice. Overexpression of GLDC in non-tumorigenic subpopulation convert the cells to become tumorigenic. Furthermore, overexpression of GLDC in NIH/3T3 cells and human primary lung fibroblasts can transform these cells, displaying anchorage-independent growth in soft agar and tumor-forming in mice. Not only is GLDC is expressed human lung cancer, it is also up-regulated in other types of cancer, such as colon cancer. RNAi knockdown of GLDC in colon cancer cell line, CACO-2 cells, can also inhibit the tumor formation in mice. Thus GLDC maybe a new metabolic target for treatment of lung cancer, and other cancers.

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