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Casiopeina II-gly and bromo-pyruvate inhibition of tumor hexokinase, glycolysis, and oxidative phosphorylation.

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Abstract

The copper-based drug Casiopeina II-gly (CasII-gly) shows potent antineoplastic effect and diminishes mitochondrial metabolism on several human and rodent malignant tumors. To elucidate whether CasII-gly also affects glycolysis, (a) the flux through the complete pathway and the initial segment and (b) the activities of several glycolytic enzymes of AS-30D hepatocarcinoma cells were determined. CasII-gly (IC_{II} = 0.74-6.7 μM) was more effective to inhibit 24-72 h growth of several human carcinomas than 3-bromopyruvate (3BrPyr) (IC_{II} = 45-100 μM) with no apparent effect on normal human-proliferating lymphocytes and HUVECs. In short-term 60-min experiments, CasII-gly increased tumor cell lactate production and glycogen breakdown. CasII-gly was 1.3-21 times more potent than 3BrPyr and cisplatin to inhibit tumor HK. As CasII-gly inhibited the soluble and mitochondrial HK activities and the flux through the HK-TPI glycolytic segment, whereas PFK-1, GAPDH, PGK, PYK activities and HPI-TPI segment flux were not affected, the data suggested glycogenolysis activation induced by HK inhibition. Accordingly, glycogen-depleted as well as oligomycin-treated cancer cells became more sensitive to CasII-gly. The inhibition time-course of HK by CasII-gly was slower than that of OxPhos in AS-30D cells, indicating that glycolytic toxicity was secondary to mitochondria, the primary CasII-gly target. In long-term 24-h experiments with HeLa cells, 5 μM CasII-gly inhibited OxPhos (80%), glycolysis (40%), and HK (42%). The present data indicated that CasII-gly is an effective multisite anticancer drug simultaneously targeting mitochondria and glycolysis.

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