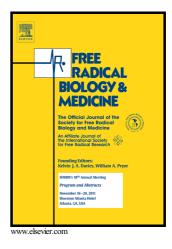
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Control of the NADPH supply for oxidative stress handling in cancer cells

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Abstract

It has not been systematically analyzed whether the NADPH supply is a limiting factor for oxidative stress management in cancer cells. In the present work, it was determined in noncancer and cancer cells the protein contents and kinetomics of (i) the cytosolic enzymes responsible for the NADPH production (*i.e.*, Glc6PDH, 6PGDH, ME, IDH-1); and (ii) the two main enzymes responsible for NADPH/NADP⁺ and GSH/GSSG recycling (GR, GPx-1) associated to oxidative stress management. With these data, kinetic models were built and further validated. Rat liver and hepatoma AS-30D cytosolic fractions exhibited greater Vmax for IDH-1 than for Glc6PDH and 6PGDH whereas human cancer cells and platelets showed greater Vmax for Glc6PDH than for 6PGDH and IDH-1. The ME activity was comparatively low in all cell types tested. The Km values for the respective specific substrates were all similar among the different cell types. Most activities were lower in AS-30D cells than in liver. In contrast, IDH-1, GIc6PDH and GR activities in human cancer cells were similar or greater to those of platelets, but GPx-1 activity was severely suppressed, despite showing similar GPx-1 protein content vs. platelets. Kinetic analysis and pathway modeling revealed a previously unveiled feedback IDH-1 regulation by GSH. The oxidative stress management in cancer cells (i) was mainly controlled by GPx-1 and the main NADPH provider was Glc6PDH; and (ii) modeling indicated that NADPH supply was not a controlling step. These data suggested that Glc6PDH and GPx-1 are adequate and promising targets for anti-cancer therapeutic intervention.

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