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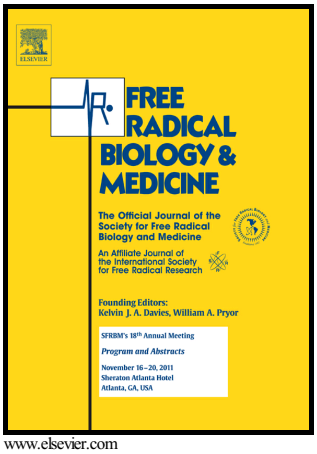

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Control of the NADPH supply for oxidative stress handling in cancer cells

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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 non-cancer 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, Glc6PDH 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.