

ANALYSIS OF THE NADH-FUMARATE REDUCTASE SYSTEM IN MITOCHONDRIAL ENERGY METABOLISM UNDER THE TUMOR MICROENVIRONMENT AS A TARGET OF NOVEL ANTICANCER THERAPY

Eriko Tomitsuka¹, Kiyoshi Kita², Hiroyasu Esumi¹

(¹Natl. Cancer Center Res. Inst. East, ²Dept. Biomed. Chem., Univ. Tokyo)

The increase of glycolysis is the principal explanation of how cancer cells produce energy in hypoxia. However, in the hypovascular tumors, starvation of critical nutrients, such as glucose, and hypoxia are observed, glycolysis alone cannot explain how cancer cells maintain their required energy levels under such conditions. To understand energy metabolism in tumor cells under the tumor microenvironment, we noticed NADH-fumarate reductase system, which exists in anaerobic species such as parasitic helminthes. This system is composed of complex I (NADH-ubiquinone reductase) and a reverse reaction of complex II (succinate ubiquinone reductase) as the oxidative phosphorylation system in mitochondria, but there is no report whether the system exists in any mammalian species.

We measured mitochondrial NADH-fumarate reductase activity in human cancer cells which were cultured under varying conditions. Cells that had been cultured under ordinary conditions had relatively low activity, but the activity increased when cells were cultured under tumor microenvironment-mimicking condition where both oxygen and glucose were deprived. The increase of NADH-fumarate reductase activity was observed with the increase activity of fumarate reductase, which is the reverse reaction of complex II regulated by phosphorylation of its subunit [Tomitsuka et al., Proc. Jpn. Acad., Ser. B 85, 258, 2009]. Moreover, the NADH-fumarate reductase system generated mitochondrial membrane potentials, which wasn't inhibited by a complex IV inhibitor, indicating that the NADH-fumarate reductase system can synthesize ATP.

Pyrvinium pamoate, an anthelmintic, has shown as anti-cancer compound in human cancer cells [Esumi et al., Cancer Sci., 95, 685, 2004]. One of the biological mechanisms of pyrvinium pamoate is the inhibition of NADH-fumarate reductase system. Pyrvinium pamoate showed the inhibition of NADH-fumarate reductase activity and also the loss of mitochondrial membrane potential generated by fumarate respiration.

Therefore, NADH-fumarate reductase system is important in maintaining mitochondrial energy metabolism under the tumor microenvironment, and that system is a novel target of anti-cancer therapy.