Role of lactic acidosis in the metabolic reprogramming in cholangiocarcinoma

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Abstract: Cancer cells produce energy via glycolysis rather than oxidative phosphorylation, leading to the increased production of lactate. The transcendent lactates in cancer cells are exported extracellularly resulting in a high lactate and low pH in the cancer environment, known as lactic acidosis. This study is aimed to determine the effects of lactic acidosis on progression and metabolism in cholangiocarcinoma (CCA) cell lines. Cell proliferation and migration were investigated for cancer progression and the oxygen consumption rate was observed for metabolic analysis using XFe24 extracellular flux analyzer. CCA cells were cultured in long term lactic acidosis. Comparing with the control cells cultured in normal glucose media, CCA cells under lactic acidosis had a reduced growth rate and colony formation but an increased cell motility. In addition, cells under lactic acidosis had a shift of metabolism from glycolysis to oxidative phosphorylation with an up-regulation of mitochondria biogenesis. The RNA sequencing and gene set enrichment analyses of the control and lactic acidosis cells revealed the gene set of epithelial mesenchymal transition, were activated in the lactic acidosis cells. Thrombospondin 1 (THBS1) was selected to further study as the highest expression in this gene set. THBS1 was up regulated in lactic acidosis cells and silencing of THBS1 resulting in the inhibition of cell proliferation, migration, and oxidative phosphorylation. Moreover, CCA patients with high THBS1 expression show poor survival compared with low expression. THBS1 might be used as the prognostic marker for CCA.

Keywords: lactic acidosis, metabolic reprogramming, cholangiocarcinoma