学位論文抄録
Abstract of Thesis

Lactic acidosis induces metabolic and phenotypic reprogramming in cholangiocarcinoma cells via the upregulation of THBS1
(乳酸アシドーシスは THBS1 発現誘導を介して胆管がん細胞の代謝リプログラミングを促進する)

タムロングワラングーン ウボンラット

UBONRAT THAMRONGWARANGGOON

Department of Medical Cell Biology, Medical Sciences Major,
Doctoral Course of the Graduate School of Medical Sciences,
Kumamoto University

Academic advisor

Professor NAKAO Mitsuyoshi

Department of Medical Cell Biology, Medical Sciences Major,
Doctoral Course of the Graduate School of Medical Sciences,
Kumamoto University

Abstract of the Thesis

Background and Purpose: Cholangiocarcinoma (CCA) is a tumor which arises from the bile duct epithelia. In general, cancer cells coordinate glucose metabolism and cell cycle to assure sufficient ATP and anabolic substrates for phases of the cell cycle. It has been shown that several proteins related with glycolytic pathway, i.e., glucose transporter 1 (GLUT1), hexokinase 2, pyruvate kinase M 2 and lactate dehydrogenase A are over-expressed in CCA and associated with cell proliferation, migration, and anti-cell death. The collective evidence indicated the association of high glycolytic rate with the progression of CCA.

Methods: CCA cells was treated with lactic acidosis media to generate lactic acidosis cells with short (SLA) and long (LLA) treatment. Lactic acidosis was determined the phenotypic change and metabolic reprogramming. To understand the effect of lactic acidosis, lactic acidosis cells was performed the RNA sequencing compared with control cells. The selected protein, Thrombospondin 1 (THBS1) was next investigated on CCA cell both lactic acidosis cells and control cells for cell proliferation, migration, and metabolic reprogramming. The expression of THBS1 in CCA patient tissues was determined by immunohistochemistry.

Results: CCA cells were created and grown under the lactic acidosis conditions, with standard glucose media serving as the control. When compared to control cells, CCA cells in SLA and LLA had decreased cell growth and colony formation while exhibiting increased cell motility. Additionally, substantial levels of oxidative phosphorylation were seen in LLA cells along with an increase in mitochondrial biogenesis. The differentially expressed genes in LLA and control cells were analyzed using RNA sequencing to investigate the mechanism by which LLA causes CCA progression and metabolic reprogramming. LLA cells increased genes related to cell migration and the epithelial-mesenchymal transition (EMT), including thrombospondin-1 (THBS1), which is a pro-EMT protein. The inhibition of THBS1 using siRNA reduced cell motility and respiratory capacity in LLA cells. Furthermore, low survival was linked to elevated THBS1 expression in CCA patients. Overall, our research indicates that LLA promotes phenotypic changes that advance CCA by upregulating THBS1 expression.

Conclusions: Overall, our research indicates that LLA promotes phenotypic changes that advance CCA by upregulating THBS1 expression.