学位論文抄録

Hyperglycaemia induces metabolic reprogramming into a glycolytic phenotype and promotes epithelial–mesenchymal transitions via YAP/TAZ–Hedgehog signalling axis in pancreatic cancer
（高血糖は膵癌に代謝的リプログラミングを誘導し、YAP/TAZ–Hedgehog シグナル軸を介して上皮間葉系転移を促進する）

柳　昭

熊本大学大学院医学教育部博士課程医学専攻消化器外科学

指導教員

馬場　秀夫　教授

熊本大学大学院医学教育部博士課程医学専攻消化器外科学

Abstract of the Thesis

Background and Purpose: Hyperglycemia is a well-known initial symptom in patients with pancreatic ductal adenocarcinoma (PDAC). Metabolic reprogramming in cancer, described as the Warburg effect, can induce epithelial-mesenchymal transition (EMT).

Methods: Biological impact of hyperglycemia on malignant behavior in PDAC was examined by in vitro and in vivo experiment. Clinical impact of hyperglycemia was investigated by immunohistochemical staining in patients with PDAC resection.

Results: Hyperglycemia promoted EMT by inducing metabolic reprogramming into a glycolytic phenotype via yes-associated protein (YAP)/PDZ-binding motif (TAZ) overexpression, accompanied by GLUT1 overexpression and enhanced phosphorylation Akt in PDAC. In addition, hyperglycemia enhanced chemoresistance by upregulating ABCB1 expression, and triggered PDAC switch into pure-basal-like subtype with activated Hedgehog pathway (GLI1 high, GATA6 low expression) through YAP/TAZ overexpression. PDAC is characterized by abundant stroma that harbors tumor-promoting properties and chemoresistance. Hyperglycemia promotes production of collagen fiber-related proteins (fibronectin, fibroblast activation protein, COL1A1, and COL11A1) by stimulating YAP/TAZ expression in cancer-associated fibroblasts (CAFs). Knockdown of YAP and/or TAZ or treatment with YAP/TAZ inhibitor (K975) abolished EMT, chemoresistance, and a favorable tumor microenvironment even under hyperglycemic conditions in vitro and in vivo.

Conclusions: Hyperglycemia induces metabolic reprogramming into glycolytic phenotype and promotes EMT via YAP/TAZ-Hedgehog signaling axis, and YAP/TAZ could be a novel therapeutic target in PDAC.