学位論文抄録

Nrf2 promotes oesophageal cancer cell proliferation via metabolic reprogramming and detoxification of reactive oxygen species

（食道癌においてNrf2はグルタチオン代謝への代謝リプログラミングを介して細胞増殖を促進する）

北野　雄希

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: Cancer cells consume a large amount of energy and maintain high levels of anabolism to promote cell proliferation via metabolic reprogramming. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a master transcription regulator of stress responses and promotes metabolic reprogramming to support cell proliferation in various types of cancer. As esophageal cancer is one of the most aggressive gastrointestinal cancers, we aimed to clarify the effect of Nrf2 on metabolic reprogramming in esophageal cancer.

Methods: The relationship between Nrf2 expression and clinical outcome was evaluated using a database comprising 201 esophageal cancers. Using *in vitro* assays and metabolome analysis, we examined the mechanism by which Nrf2 affects malignant phenotype.

Results: High immunohistochemical expression of Nrf2 was significantly associated with poor recurrence-free survival (HR=2.67, P=0.0004) and overall survival (HR=2.90, P<0.0001) in esophageal cancer patients. In an *in vitro* assay with siRNA, Nrf2 depletion significantly decreased cell growth and enhanced G1 cell cycle arrest and apoptosis. In addition, reactive oxygen species (ROS) were not removed by detoxification via the Nrf2 pathway, with concomitant induction of the p38 mitogen-activated protein kinase pathway. The metabolome analysis showed that Nrf2 strongly promoted metabolic reprogramming to glutathione metabolism, which synthesizes the essential fuels for cancer progression. Furthermore, metabolome analysis using esophageal cancer specimens confirmed that samples displaying high Nrf2 expression promoted glutathione synthesis. The mechanism Nrf2 promoted glutathione metabolism was that Nrf2 regulated the levels of main enzymes (GCLM, GCLC, and xCT) catalyzing glutathione synthesis.

Conclusion: Metabolic reprogramming to glutathione metabolism, and ROS detoxification by activation of Nrf2, enhanced cancer progression and led to poor clinical outcome in esophageal cancer patients.