学位論文　全文要約

Establishment of oxaliplatin-resistant gastric cancer organoids: importance of myoferlin in the acquisition of oxaliplatin resistance
（オキサリプラチン耐性胃がんオルガノイドの樹立及びオキサリプラチン耐性獲得における Myoferlin の意義）

主指導教員：酒井　規雄教授
（医系科学研究科　神経薬理学）
副指導教員：大上　直秀教授
（医系科学研究科　分子病理学）
副指導教員：宮内　睦美教授
（医系科学研究科　口腔顎顔面病理病態学）

原田　健司

（医系科学研究科　医歯薬学専攻）

全文要約（Abstract）

Background

The attainment of drug resistance in gastric cancer (GC) is a problematic issue. Although many studies have shown that cancer stem cells (CSCs) play an important role in the acquisition of drug resistance, there is no clinically available biomarker for predicting oxaliplatin (L-OHP) resistance in relation to CSCs. Organoid technology, a novel 3D cell culture system, allows harboring of patient-derived cancer cells containing abundant CSCs using niche factors in a dish.

Methods

In this study, we established L-OHP-resistant gastric cancer organoids (GCOs) and evaluated their gene expression profile using microarray analysis. We validated the upregulated genes in the L-OHP-resistant GCOs compared to their parental GCOs to find a gene responsible for L-OHP resistance by qRT-PCR, immunohistochemistry, in vitro, and in vivo experiments.

Results

We found myoferlin (MYOF) to be a candidate gene through microarray analysis. The results from cell viability assays and qRT-PCR showed that high expression of MYOF correlated significantly with the IC50 of L-OHP in GCOs. Immunohistochemistry of MYOF in GC tissue samples revealed that high expression of MYOF was significantly associated with poor prognosis, T grade, N grade, and lymphatic invasion, and showed MYOF to be an independent prognostic indicator, especially in the GC patients treated with platinum-based chemotherapy. The knockdown of MYOF repressed L-OHP resistance, cell growth, stem cell features, migration, invasion, and in vivo tumor growth.

Conclusions

Our results suggest that MYOF is highly involved in L-OHP resistance and tumor progression in GC. MYOF could be a promising biomarker and therapeutic target for L-OHP-resistant GC cases.

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