別表６
（３）

Keio University

Thesis Abstract

No.

Registration Number	☑ "KOU" □ "OTSU" No. *Office use only	Name	Mahawongkajit Prasit

Thesis Title

miR-125a-5p expression was associated with docetaxel resistance through regulation of the *ICIS/MCAK* pathway in esophageal squamous carcinoma cells

(食道扁平上皮癌細胞のドセタキセル耐性に関わる*ICIS/MCAK*経路における*miR-125a-5p*の関与による制御)

Thesis Summary

The addition of docetaxel (TXT) as a third agent to cisplatin/5-FU (DCF) therapy has reportedly enhanced antitumor activity. However, the prognosis of patients with drug resistance is poor. Recent studies have shown the involvement of several miRNAs in resistance to anticancer treatment. The aim of the study was to investigate whether the study could predict a tumor's response to docetaxel by analyzing miRNA expression profiles and their functions in human esophageal squamous carcinoma cell (ESCC) lines.

Docetaxel-resistant (TXTR) cells were established from parental cells by exposing them to gradually increasing docetaxel concentrations. Two resultant human ESCC cell lines were resistant to docetaxel, with IC50 values of 2.82 ± 0.29 nmol (line TE8-TXTR) and 4.61 ± 0.37 nmol (line TE11-TXTR). In comparison, the parental cells of TE8 and TE11 had IC50 values of 0.15 ± 0.05 nmol and 1.33 ± 0.08 nmol, respectively. Target miRNA and mRNA were analyzed in databases (MicroRNA.org and miRBase). Docetaxel-resistant cells were assessed by RT-PCR and quantitative PCR. The results found downregulation of *miR-125a-5p* (target miRNA) and showed increased expression of the inner centromere KinI stimulator *(ICIS*) / mitotic centromere-associated kinesin (*MCAK*) pathway. *ICIS* and *MCAK* play important roles in microtubule depolymerization in the mitotic phase of cell proliferation. Next, using the parental cell lines with upregulated *miR-125a-5p* and decreased expression of *ICIS* and *MCAK*, the parental cells were transfected with a specific inhibitor of *miR-125a-5p*. The results indicated a significant increase in the live cell populations in apoptosis assays.

In this study, the downregulation of *miR-125a-5p* enhanced the resistance to docetaxel by interfering with the microtubule network via regulation of *ICIS* protein expression. This study demonstrated a role of *miR-125a-5p* and gene target *ICIS* in modulating docetaxel sensitivity.