博士論文（要約）

Identification of a marker for gastric cancer cell fractions and a marker for predicting sensitivity to a DNA demethylating agent

（胃がん細胞含有率測定およびDNA脱メチル化剤感受性予測のための分子マーカーの同定）

宗亮

ABSTRACT

Gastric cancer is one of the major causes of cancer-related deaths worldwide, and the 5-year overall survival for patients with advanced gastric cancer remains very poor. The molecular mechanisms of gastric carcinogenesis are still not fully understood, but the importance of epigenetic alterations is now clear. Therefore, in this study, I aimed i) to develop a molecular marker to assess the cancer cell fraction in any DNA sample, which will facilitate investigations of molecular mechanisms, and ii) to develop a marker that can predict gastric cancers that will respond to DNA demethylating agents. To establish a DNA methylation marker to estimate the cancer cell fraction, I isolated genomic regions that were specifically methylated in gastric cancer cells. I further identified *OSR2*, *PPFIA3*, and *VAV3* as barely methylated in normal cells and highly methylated in cancer cells. The cancer cell fraction assessed by the panel of these three genes showed good correlation with that assessed by the *TP53* mutant allele frequency in 13 gastric cancers. After correction of the gastric cancer cell fraction, unsupervised clustering analysis of the genome-wide DNA methylation profiles yielded clearer clustering. To identify a sensitivity marker to 5-aza-2′-deoxycytidine (5-Aza-CdR), I first identified six and seven gastric cancer cell lines that were sensitive and resistant, respectively, to 5-Aza-CdR. By comprehensive gene expression analysis, *LINC00162* was identified to be highly expressed in sensitive cell lines. Knock-down of *LINC00162* in sensitive cell lines decreased their sensitivity to 5-Aza-CdR, whereas its overexpression in resistant cell lines increased their sensitivity. *In vivo* experiment, overexpression of *LINC00162* increased the sensitivity to 5-Aza-CdR. Taken together, our new DNA methylation marker for cancer cell fractions will help advance the molecular characterization of gastric cancers, and our new sensitivity marker, *LINC00162*, may be useful to stratify gastric cancer patients for 5-Aza-CdR treatment.