論 文 審 査 の 結 果 の 要 旨

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（論文審査の結果の要旨）

The cure rate of childhood acute lymphoblastic leukemia (ALL) has improved over the past four decades. However, the prognosis of approximately 20% of patients with ALL remains poor because of disease recurrence. In recent years, many studies have attempted to identify new clinical biomarkers that can predict high-risk patients and serve as targets for novel therapeutic interventions using gene-expression microarrays, DNA-methylation arrays, and next-generation sequencing. DNA methylation and histone modifications are two major epigenetic mechanisms regulating gene expression. Hypermethylation of CpG islands in the promoter region of tumor suppressor genes that results in transcriptional silencing plays an important role in lymphoid-lineage leukemogenesis and may be an important contributor toward relapse. In addition, DNA methylation profiling is useful for subtype classification of newly diagnosed ALL patients and prediction of outcome and relapse risk.

In this study, we present the results as follows:

1) According to genome wide methylation of analysis of a patient with relapsed B-cell precursor ALL, cadherin superfamily genes were hypermethylated at relapse, showing the genes as the top candidate genes with aberrant methylation at relapse.

2) Methylation status of cadherin superfamily genes in B-cell precursor ALL: *Cadherin (CDH)1* and *protocadherin (PCDH)8* methylation was observed in all 6 leukemic cell lines, whereas *PCDH17* methylation was detected in 4 of them. In 40 B-cell precursor (BCP) ALL samples at onset, the methylation frequencies of *CDH1*, *PCDH8*, and *PCDH17* were 62.5%, 55%, and 30%, respectively. However, *CDH1* and *PCDH8* methylation was also detected in 80% and 20% of control BM samples, respectively. On the contrary, *PCDH17* was unmethylated in all control BM samples.

3) The relationship between methylation status of cadherin superfamily genes at diagnosis and clinical characteristics of patients with B-cell precursor ALL: Event-free survival (EFS) of *PCDH17* methylation-positive group was profoundly inferior to that of *PCDH17* methylation-negative group: 33% (95% CI, 10–59) vs. 75% (95% CI, 55–87); $P = 0.005$. A significant difference in the overall survival (OS) was also found between the two groups: 50% (95% CI, 21–73) vs. 82% (95% CI, 62–92); $P = 0.016$. Conversely, there were no substantial correlations between the methylation status of *CDH1* and EFS or OS, and between the methylation status of *PCDH8* and EFS or OS. By univariate and multivariate analyses, only *PCDH17* methylation was associated with increased risk for relapse and mortality in patients with BCP ALL [HR, 5.23; $P = 0.016$ for relapse and HR, 8.22; $P = 0.016$ for mortality]. However, *CDH1* and *PCDH8* methylation did not influence ALL outcomes.

4) There was no correlation between *PCDH17* methylation and mRNA expression levels in ALL samples and cell lines.

Conclusion: *PCDH17* methylation at onset was closely related to poor prognosis, and thus it could be used as a new biomarker to predict relapse in BCP ALL.

以上の内容により、主査、副査は一致して本論文を学位論文として価値があるものと認めた。