News Release

Title
A novel MEF2D-BCL9 fusion gene in high-risk leukemia

Key Points
○ We identified a novel MEF2D-BCL9 fusion gene as a cause of acute lymphoblastic leukemia (ALL) in adolescents.
○ Although MEF2D-BCL9–positive ALL exhibited refractory disease, we showed that several molecular targeted drugs had reliable anti-leukemic effects.
○ This fusion gene is a potent biomarker in high-risk ALL and molecular targeted therapy is expected to improve the outcome.

Summary
Emeritus Prof. Seiji Kojima, Dr. Hideki Muramatsu, and Dr. Kyogo Suzuki in Department of Pediatrics, Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.), Dr. Yusuke Okuno in Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, and their colleagues identified a novel MEF2D-BCL9 fusion gene in acute lymphoblastic leukemia (ALL) in adolescents.

ALL makes up a significant proportion of pediatric cancers and is a leading cause of cancer-associated deaths in children. To elucidate critical genetic events in relapsed or primary refractory ALL, we enrolled 59 pediatric patients and performed comprehensive genetic analysis using next-generation sequencing technology.

As a result, we identified a novel fusion gene involved identical combination of MEF2D and BCL9 in four cases. All MEF2D-BCL9–positive patients were with B-cell precursor immunophenotype and characterized as adolescents, being resistant to conventional chemotherapy, and having unique leukemic blasts with marked vacuole. Exogenous expression of MEF2D-BCL9 in an ALL cell line promoted cell growth and induced resistance to corticosteroid. We also showed that several molecular targeted drugs including histone deacetylase inhibitor and proteasome inhibitor exhibited anti-leukemic effects in vitro.

A MEF2D-BCL9 fusion gene is a potent biomarker in high-risk ALL. In addition, incorporation of molecular targeted drugs to the treatment of MEF2D-BCL9–positive ALL is a promising strategy and contributes to improvement of the outcome.

This work was supported by Project Mirai Cancer Research Grants, which was provided by Japan Cancer Society.
Research Background

Acute lymphoblastic leukemia (ALL) is the most common hematological malignancy in childhood. A significant improvement in treatment outcome in pediatric ALL was achieved by incorporation of precise risk stratification, combined chemotherapy approaches, allogeneic hematopoietic stem cell transplantation, and, in BCR-ABL1–positive ALL, the clinical use of tyrosine kinase inhibitors. The 5-year overall survival rate of childhood ALL has reached approximately 90% in developed countries. However, a considerable number of patients still experience relapse, for which the prognosis is often very poor. To tackle current issues in ALL, we applied comprehensive transcriptome analysis to patients with relapsed/refractory ALL to identify genetic alterations that may contribute to the improvement of treatment outcome.

Research Results

We performed RNA sequencing analysis in 59 children with relapsed or primary refractory ALL. Among them, we identified a novel MEF2D-BCL9 fusion gene in four patients. Both MEF2D and BCL9 are located on chromosome 1 and the distance between these two genes is approximately 9 Mb, which is too small for chromosomal aberrations to be detected by G-banding. We identified genomic breakpoints and confirmed that inversion in this chromosomal region resulted in this fusion (Figure 1).

All four patients with MEF2D-BCL9 had similar clinical characteristics, including the onset in adolescents (range, 10 to 13 years old), the diagnosis of B-cell precursor ALL based on a CD19+ CD20- HLA-DR+ immunophenotype, very early relapse, and uniform morphological findings (Figure 2). Gene expression profiles assessed by clustering analysis revealed that leukemic cells with MEF2D-BCL9 grouped into a compact cluster distinguishable from those with other types of ALL. These findings suggested that this fusion gene characterizes a distinctive subset of ALL. As there was no obvious driver mutation detectable by whole-exome sequencing in all four patients, MEF2D-BCL9 itself was presumed to have oncogenic potency.

In functional analysis, exogenous expression of MEF2D-BCL9 in an ALL cell line promoted cell growth and induced resistance to corticosteroid, one of the key drugs in the treatment of ALL. On the other hand, we also showed that several molecular targeted drugs including histone deacetylase inhibitor and proteasome inhibitor, which were already available in clinical settings, exhibited anti-leukemic effects in vitro.
Figure 1. MEF2D-BCL9 fusion gene
Inversion in a small region of chromosomal 1 results in MEF2D-BCL9 gene fusion.

Figure 2. Leukemic cells harboring MEF2D-BCL9 fusion gene
MEF2D-BCL9–positive ALL is morphologically characterized by large, densely basophilic, and heavily vacuolated (△) leukemic blasts.
Research Summary and Future Perspective

A MEF2D-BCL9 fusion gene is a potent biomarker in high-risk ALL. In addition, incorporation of molecular targeted drugs to the treatment of MEF2D-BCL9–positive ALL and development of novel molecular targeted therapies are expected to improve the outcome.

Publication

Japanese ver.