

News Release

Title

MYB rearrangements in blastic plasmacytoid dendritic cell neoplasm

Key Points

- **We identified MYB rearrangements as a cause of blastic plasmacytoid dendritic cell neoplasm (BPDCN).**
- **This mutation can be a potent biomarker and we established a diagnostic technique for BPDCN.**
- **Several molecular targets identified in this study may improve treatment outcomes.**

Summary

Designated lecturer Yusuke Okuno and Associate Prof. Seiichi Kato in Center for Advanced Medicine and Clinical Research, Nagoya University Hospital (Director: Naoki Ishiguro, M.D., Ph.D.), Dr. Kyogo Suzuki in Department of Pediatrics, Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.), and their colleagues identified MYB rearrangements as a causative mutation in blastic plasmacytoid dendritic cell neoplasm (BPDCN).

BPDCN is a rare hematological malignancy derived from plasmacytoid dendritic cell precursors, which is characterized by frequent skin involvement, an aggressive clinical course, and a dismal prognosis. To elucidate critical genetic events in BPDCN, we enrolled 14 patients and performed comprehensive genetic analysis using next-generation sequencing.

We identified novel and recurrent MYB gene rearrangements in all five evaluated pediatric patients (100%) and four of nine adult patients (44%) with BPDCN as a causative mutation. These rearrangements resulted in the formation of several fusion genes (MYB-*PLEKHO1*, -*ZFAT*, -*DCPS*, and -*MIR3134*) and the truncation of negative regulatory domain of MYB, leading to constitutive MYB transcriptional activation. We confirmed that this aberration can be a potent diagnostic marker for BPDCN, and identified some molecular targets in the context of this disease mechanism.

Our findings provide biological interest regarding MYB in tumorigenesis and critical insights into the pathogenesis and therapeutic investigation of BPDCN.

Research Background

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological malignancy that is derived from plasmacytoid dendritic cell precursors. BPDCN tends to occur in elderly people with frequent skin involvement (Figure 1) and is associated with an aggressive clinical course and a poor prognosis. Although optimized diagnostics and therapies should improve patient outcomes, the pathobiological and genetic aspects of BPDCN remain unclear. Our study was aimed to identify a critical genetic event in BPDCN, which could provide better understanding of BPDCN pathogenesis.



Figure 1: Skin involvement of BPDCN

This patient presented dark red, nodular skin lesion (ϕ 2cm).

Research Results

This study included 14 patients (five children and nine adults) with BPDCN. We performed comprehensive transcriptome analysis using next-generation sequencing and identified recurrent gene rearrangements that involved the MYB proto-oncogene in all five pediatric patients (100%) and four of nine adult patients (44%). The resulting fusion genes included MYB-*PLEKHO1*, MYB-*ZFAT*, MYB-*DCPS*, and MYB-*MIR3134*, none of which have been previously reported to the best of our knowledge (Figure 2). Consequent to the rearrangement, the negative regulatory domain of MYB was truncated, leading to constitutive MYB transcriptional activation, as described in other malignancies.

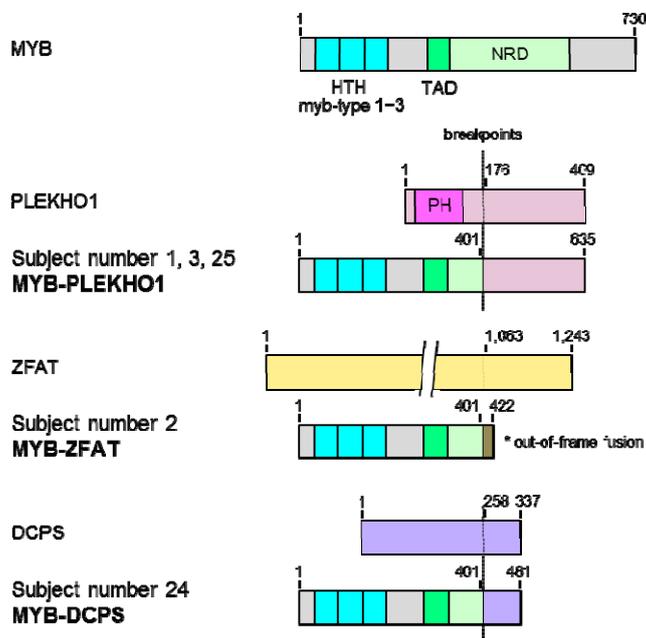


Figure 2: Predicted domain structures of chimeric proteins.

Dotted lines indicate breakpoints. HTH, helix-turn-helix; NRD, negative regulatory domain; PH, pleckstrin homology domain; TAD, transcriptional activation domain.

We also performed whole-exome or targeted sequencing in the search of point mutations for all patients. This analysis revealed that children were not found to carry any identifiable driver mutations, whereas all adult patients harbored at least one point mutation in genes such as TET2, ASXL1, IKZF1, ZRSR2, NRAS, and EZH2, most of which were reported to be mutated in BPDCN and myeloid malignancies. These results suggest that BPDCN has biologically different aspects between pediatric and adult patients, and this may affect their treatment strategies.

We further analyzed the biological consequence of this aberration. Exogenous MYB-*PLEKHO1* expression in an established cell line (HEK 293T cells) led to the upregulation of several known downstream targets of MYB. The identified significantly upregulated genes included cell surface molecule-encoding genes such as CXCR4, CD68, CD363, and CD355, possibly providing targets for antibody-mediated anticancer therapies.

The translocations corresponding to these fusions were not detected by the conventional metaphase analysis except in one patient with t(1;6), who harbored MYB-*PLEKHO1*. However, we confirmed that fluorescence in situ hybridization (FISH) analysis efficiently detected the breaking apart of MYB in formalin-fixed, paraffin-embedded sections (Figure 3). This analysis can constitute a valuable diagnostic tool for detecting of MYB rearrangements in BPDCN.

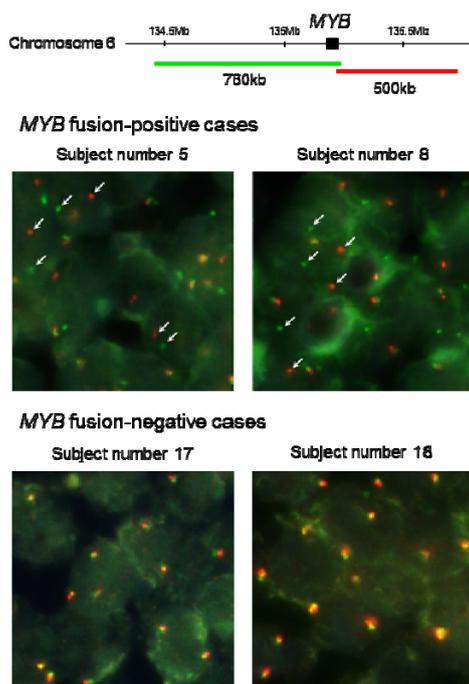


Figure 3: FISH analysis

Green and red probes were used to detect targets upstream and downstream of MYB. White arrows indicate split signals, indicating the presence of MYB rearrangement.

Research Summary and Future Perspective

We expect that our findings provide critical insights regarding BPDCN pathogenesis and contribute to molecular biology-oriented diagnostic techniques and molecular-targeted therapies for

this intractable malignancy.

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/material/nu_medical/res/topix/2016/leukemia_20170327jp.pdf