News Release

Title

Novel *NIPBL-BEND2* fusion gene identified in osteoblastoma-like phosphaturic mesenchymal tumor of the fibula

Key Points

• We found a novel *NIPBL-BEND2* fusion gene in osteoblastoma-like phosphaturic mesenchymal tumor of the fibula.
• Our results suggest that this novel *NIPBL-BEND2* fusion gene promotes cell proliferation possibly via the MYC pathway and might be one of the etiologies of PMTs other than *FN1-FGFR1* or *FN1-FGF1*.

Summary

Tomohisa Sakai, assistant professor of Rare Cancer Center, Nagoya University Hospital, and Yoshihiro Nishida, professor of Department of Rehabilitation Medicine, Yusuke Okuno, professor of Department of Virology, Nagoya City University Graduate School of Medical Science, reported a novel *NIPBL-BEND2* fusion gene in osteoblastoma-like phosphaturic mesenchymal tumor of the fibula.
Phosphaturic mesenchymal tumor (PMT) is a rare tumor that secretes fibroblast growth factor 23 (FGF23) and causes hypophosphatemia and tumor-induced osteomalacia (TIO). Fusion genes *FN1-FGFR1* and *FN1-FGF1* have been detected in some PMTs, but the pathogenesis of PMTs without these fusion genes remains unclear. We performed RNA sequencing the case of osteoblastoma-like phosphaturic mesenchymal tumor of the fibula. As a result, *FN1-FGFR1* and *FN1-FGF1* were not detected, but a novel *NIPBL-BEND2* fusion gene was identified. When we forcedly expressed this fusion gene in HEK293T cells and MG63 cells, cell proliferation was enhanced in both cell lines. Furthermore, Gene set enrichment analysis of HEK293T cells showed significant upregulation of MYC-target genes. Our results suggest that this novel *NIPBL-BEND2* fusion gene promotes cell proliferation possibly via the MYC pathway and might be one of the etiologies of PMTs other than *FN1-FGFR1* or *FN1-FGF1*.

Research Background

Phosphaturic mesenchymal tumor (PMT) is an extremely rare neoplasm that causes tumor-induced osteomalacia (TIO) in most affected patients, usually through the production of fibroblast growth factor 23 (FGF23). In 1987, the

term “phosphaturic mesenchymal tumor” was first proposed and classified into four morphological variants: mixed connective tissue, osteoblastoma-like, nonossifying fibroma-like, and ossifying fibroma-like. It was also reported that PMT is the most common cause of TIO, accounting for 80% of the total. PMT was adopted as a single entity of uncertain differentiation soft tissue tumor in the 5th edition of the WHO 2020 classification. However, a significant number of cases also occur in bone.

The fusion gene in PMT was first reported in 2015, and *FN1-FGFR1* was found in 11 of 15 PMTs. Next, the fusion gene *FN1-FGF1* was reported in 2016, with a report showing *FN1-FGFR1* in 42% (21/50) and *FN1-FGF1* in 6% (3/50) of 50 PMTs. These fusion genes are thought to promote hypophosphatemia by enhancing the secretion of FGF23 via a mutant ligand or a mutant receptor in the FGF1-FGFR1 pathway. However, these fusion genes have been identified in fewer than half of PMTs, and the pathogenesis of the other PMTs remains unknown.

Research Results

We performed RNA sequencing using a resected specimen from the patient with osteoblastoma-like phosphaturic mesenchymal tumor of the fibula and identified a novel in-frame fusion involving *NIPBL* (encoding Nipped-B gene product and fungal Scc2-type sister chromatid cohesion proteins) and *BEND2* (encoding a protein which has two BEN domains in the C-terminus). The fusion protein contained the phosphorylation site derived from *NIPBL* and the BEN domain derived from *BEND2*. In polymerase chain reaction, the amplification of target regions containing breakpoint of the chromosomal structure was confirmed using two primer sets in tumor DNA of the PMT.

We cloned and transfected the *NIPBL-BEND2* fusion gene to HEK293T and MG63 osteoblast lineage cell line. The *NIPBL-BEND2* transfected cells showed faster proliferation at 48 hours after transfection ($p = 0.001$ and 0.003, Student’s t-test, respectively.). A gene set enrichment analysis of the fusion gene-introduced HEK293T cells identified a significant enrichment of MYC-target genes, consistent with faster proliferation. However, the expression of FGF23 (log2 fold change; 0.031) and FGFR1 (log 2 fold change; 1.59) was not changed significantly by the transfection.

Research Summary and Future Perspective

Our results suggest that this novel *NIPBL-BEND2* fusion gene promotes cell proliferation possibly via the MYC pathway and might be one of the etiologies of PMTs other than *FN1-FGFR1* or *FN1-FGF1*.

To verify the hypothesis, it is necessary to accumulate more cases of PMTs and

performed further research.

Publication

Case report: Novel NIPBL-BEND2 fusion gene identified in osteoblastoma-like phosphaturic mesenchymal tumor of the fibula
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