Pulmonary Inflammatory Myofibroblastic Tumor Expressing a Novel Fusion, PPFIBP1–ALK: Reappraisal of Anti-ALK Immunohistochemistry as a Tool for Novel ALK Fusion Identification

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Abstract

Purpose: The anaplastic lymphoma kinase (ALK) inhibitor crizotinib has been used in patients with lung cancer or inflammatory myofibroblastic tumor (IMT), both types harboring ALK fusions. However, detection of some ALK fusions is problematic with conventional anti-ALK immunohistochemistry because of their low expression. By using sensitive immunohistochemistry, therefore, we reassessed "ALK-negative" IMT cases defined with conventional immunohistochemistry (approximately 50% of all examined cases).

Experimental Design: Two cases of ALK-negative IMT defined with conventional anti-ALK immunohistochemistry were further analyzed with sensitive immunohistochemistry [the intercalated antibody-enhanced polymer (iAEP) method].

Results: The two "ALK-negative" IMTs were found positive for anti-ALK immunohistochemistry with the iAEP method. 5'-rapid amplification of cDNA ends identified a novel partner of ALK fusion, protein-tyrosine phosphatase, receptor-type, F polypeptide-interacting protein-binding protein 1 (PPFIBP1) in one case. The presence of PPFIBP1–ALK fusion was confirmed with reverse transcriptase PCR, genomic PCR, and FISH. We confirmed the transforming activities of PPFIBP1–ALK with a focus formation assay and an in vivo tumorigenicity assay by using 3T3 fibroblasts infected with a recombinant retrovirus encoding PPFIBP1–ALK. Surprisingly, the fusion was also detected by FISH in the other case.

Conclusions: Sensitive immunohistochemical methods such as iAEP will broaden the potential value of immunohistochemistry. The current ALK positivity rate in IMT should be reassessed with a more highly sensitive method such as iAEP to accurately identify those patients who might benefit from ALK-inhibitor therapies. Novel ALK fusions are being identified in various tumors in addition to IMT, and thus a reassessment of other "ALK-negative" cancers may be required in the forthcoming era of ALK-inhibitor therapy. Clin Cancer Res; 17(10); 3341–8. ©2011 AACR.

Introduction

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that was discovered in anaplastic large cell lymphoma (ALCL) in the form of a fusion protein, NPM–ALK. (1, 2). In addition to ALCL (fused to NPM, TPM3, TPM4, ATIC, TFG, CLTC, MSN, MYH9, or ALO17; refs. 1–10), ALK has further been found to generate fusions in inflammatory myofibroblastic tumor (IMT; TPM3, TPM4, CLTC, CARS, RANBP2, ATIC, or SEC31L1; refs. 10–15), ALK-positive large B-cell lymphoma (CLTC, NPM, SEC31L1, or SQSTM1; 16–19), lung cancer (EML4 or KIF5B; refs. 20, 21), and ALK-positive histiocytosis (TPM3; ref. 22). Besides, some ALK fusions have been reported without showing histopathologic evidence: TPM4–ALK in esophageal squamous cell carcinoma (23, 24), TFG–ALK in lung adenocarcinoma (25), and EML4–ALK in colon and breast carcinomas (26). The wild-type ALK is mainly expressed in the developing nervous system, and is usually not expressed in other normal tissues (27). A fusion protein formation with a partner through chromosomal translocation is the most common mechanism of ALK overexpression and ALK kinase domain activation. These features render ALK fusion oncokinas as an ideal molecular target.

Recently, the ALK inhibitor crizotinib has been used in patients with lung cancer or IMT, both types harboring ALK fusions (28, 29). The compound showed a 57% response rate in lung cancers (28), and a strong response for several months in IMT (29). Crizotinib and other ALK inhibitors...
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Translational Relevance

Anaplastic lymphoma kinase (ALK) inhibitors have become one of the most promising groups of molecularly targeted drugs. Therefore, ALK is no longer a mere research target or simply a diagnostic marker, but is directly linked to the therapeutic benefit of patients harboring the fusions.

Pathologic diagnoses for ALK fusion-positive tumors have been made reliably with anti-ALK immunohistochemistry. Since the discovery of EML4–ALK, however, an unexpected problem in anti-ALK immunohistochemistry has become apparent, that is, the inability to detect a low level of EML4–ALK expression. To overcome this, we developed the intercalated antibody-enhanced polymer immunohistochemistry, which successfully detected EML4–ALK.

In other words, this indicates that unknown ALK fusions, particularly those expressed at a low level, may wait to be discovered in ‘ALK-negative’ tumors defined with conventional immunohistochemistry. In the forthcoming era of ALK-inhibitor therapy, ‘ALK-negative’ tumors should be reassessed with a high sensitive immunohistochemistry and, if positive, be further examined with appropriate molecular method(s).

Materials and Methods

Materials

Pathologic specimens from 2 pulmonary IMT cases, originally diagnosed as fibrous histiocytoma (1988: case 1, 45-year-old male; 1998: case 2, 34-year-old female), were reassessed morphologically and immunohistochemically. Surgically removed tumor specimens were routinely fixed in 20% neutralized formalin and embedded in paraffin for conventional histopathologic examination. For case 2, total RNA was extracted from the corresponding snap-frozen specimen and purified with the use of an RNeasy Mini kit (Qiagen). The study was approved by the institutional review board of the Japanese Foundation for Cancer Research.

Immunohistochemistry

Formalin-fixed, paraffin-embedded tissue was sliced at a thickness of 4 μm, and the sections were placed on silane-coated slides. For antigen retrieval, the slides were heated for 40 min at 97°C in Target Retrieval Solution (pH 9.0; Dako). For the conventional staining procedure, the slides were incubated at room temperature with Protein Block Serum-free Ready-to-Use solution (Dako) for 10 minutes and then with primary antibodies against ALK (5A4), CD34, cytokeratins (AE1/AE3), S100, or desmin for 30 minutes. The immune complexes were then detected with dextran polymer reagent (EnVision + DAB system; Dako) and an AutoStainer instrument (Dako). The iAEP method was also used for the sensitive detection of ALK, as described previously (21).
Isolation of PPFIBP1–ALK fusion

To obtain cDNA fragments corresponding to a novel ALK fusion gene, we used a 5′-RACE method with the SMART RACE cDNA Amplification Kit (Clontech) according to the manufacturer’s instructions, with a minor modification: the ALK2458R primer (5′-GTAGTTGGGGTTGTAGTCGGT-CATGATGGT-3′) was used as the gene-specific reverse primer.

From the oligo(dT)-primed cDNA obtained from case 2 RNA, a 471bp cDNA fragment containing the fusion point was specifically amplified with the primers PPFIBP1-592F (5′-AGAGACACAGAGGGGCTGATT-3′) and ALK3078RR (5′-ATCCAGTTGTCTGGTTCAGAGC-3′).

PCR analysis of genomic DNA for PPFIBP1–ALK in case 2 was carried out with a pair of primers flanking the putative fusion point, PPFIBP1-607F (5′-TATCTGGGTTGGAATTTGCCCCTG-3′) and Fusion-RT-AS (5′-TCTTGCCAGCAAAGCAGTAGTTGG-3′).

From the cDNA, a full-length cDNA for PPFIBP1–ALK was amplified by PCR with the PA-w-cDNA-in-S primer (5′-TATCTGGGTTGGAATTTGCCCCTG-3′) and PrimeSTAR HS DNA polymerase (TakaraBio).

FISH

FISH analysis of gene fusion was carried out with bacterial artificial chromosome (BAC) clone-derived DNA probes for ALK and PPFIBP1. Unstained sections (4 μm thick) were subjected to hybridization with an ALK-split probe set (Abbott) or BAC clone-derived probes for ALK (RP11–984121, RP11–62B19) and PPFIBP1 (RP11–1060J15). Hybridized slides were then stained with DAPI and examined with the fluorescence microscope BX51 (Olympus).

Transformation assay for ALK fusion proteins

Analysis of the transforming activity of PPFIBP1–ALK was carried out as described previously (20, 37, 38). Briefly, the pMXS-based expression plasmid for PPFIBP1–ALK, EML4–ALK variant 1, or NPM–ALK was used to generate recombinant ecotropic retrovirus, followed by individual infection of mouse 3T3 fibroblasts (39). Formation of the transformed foci was evaluated after culturing the cells for 14 days. The same set of 3T3 cells was subcutaneously injected into nu/nu mice, and tumor formation was examined after 20 days. The animal experiments were approved by the animal ethics committee of Jichi Medical University.

Results

Morphology and immunophenotype of PPFIBP1–ALK-positive IMT

Histopathologic analysis of the 2 IMT cases revealed a marked proliferation of cells composed of somewhat histiocytoid spindle cells showing a fascicular or storiform pattern. The tumor cells were uniform and had pale eosinophilic cytoplasm and an oval vesicular nucleus, within which a small nucleolus was centrally located. Mild inflammatory infiltrate containing lymphocytes, plasma cells, and foamy histiocytes was observed (Fig. 1A and 1D). The tumor cells were negative for ALK with conventional anti-ALK immunohistochemistry (B and E), but were clearly positive for ALK when the IAEP method was used. The staining pattern is diffuse cytoplasmic (C and F). Case 1 (A–C), Case 2 (D–F).
HHF35, CD34, AE1/AE3, and S100. Desmin was focally positive in case 1, but was negative in case 2.

Identification of PPFIBP1–ALK as a novel ALK fusion gene

We conducted anti-ALK immunohistochemistry on 2 morphologically typical pulmonary IMT cases, originally diagnosed as fibrous histiocytoma. Immunostaining for ALK with the conventional polymer method led to the revised diagnosis of “ALK-negative” IMT (Fig. 1B and E). In the present study, anti-ALK immunohistochemistry with the iAEP method, however, showed a diffuse positive cytoplasmic staining (Fig. 1C and F), indicating the possibility of ALK fusion to a novel partner gene, the expression level of which is modest. To address this issue, in case 2 we conducted 5'–RACE assay for the isolation of an upstream cDNA to the ALK kinase domain cDNA, for which snap-frozen material was available.

Interestingly, we isolated a cDNA fragment containing exon 8 of PPFIBP1 followed by a 49 bp-sequence within intron 19 of ALK and coupled to exon 20 of ALK (Fig. 2), suggesting the presence of a novel fusion between PPFIBP1 and ALK genes. Because insertion of the intronic 49 bp allows an in-frame fusion between the 2 genes, this rearrangement likely produces a novel fusion-type tyrosine kinase. To confirm the genomic rearrangement responsible for the PPFIBP1–ALK fusion, a genomic PCR assay (Fig. 2B) and both ALK split and PPFIBP1–ALK fusion FISH assays (Fig. 3) were carried out. All results were consistent with the presence of t(2;12)(p23;p11) leading to the generation of PPFIBP1–ALK. Owing to the limited material available in case 1, only the FISH analyses were carried out. Surprisingly, these results also indicate the presence of PPFIBP1–ALK (Fig. 3, Supplementary Fig. 2A–C).

Transforming activities of PPFIBP1–ALK

To prove that the t(2;12)(p23;p11) rearrangement leads to the production of PPFIBP1–ALK kinase, in case 2 we attempted to amplify from the cDNA a full-length cDNA encoding the protein. By using a sense primer at the 5’–untranslated region of PPFIBP1 mRNA (GenBank accession no. NM_003622) and an antisense primer at...

Figure 2. Identification of PPFIBP1–ALK: a PCR product of 471 bp covering the fusion point of PPFIBP1–ALK cDNA was specifically amplified from the tumor cells of case 2. The left lane contains DNA size standards (100 bp ladder). The right lane represents no template control (A). A PCR product of approximately 3 kbp covering the genomic fusion point of PPFIBP1–ALK was specifically amplified from the tumor cells of case 2. The left lane contains DNA size standards (1 kbp ladder). The right lane represents no template control (B). In our 5′-RACE products, exon 8 of PPFIBP1 cDNA was fused to a 49 bp sequence in intron 19 of ALK, followed by exon 20 of ALK (C). PPFIBP1 contains 5 coiled-coil domains. A chromosome translocation, t(2;10)(p23;p11), generates a fusion protein in which the top 3 coiled-coil domains of PPFIBP1 and the intracellular region of ALK (containing the tyrosine kinase domain) are conserved. Numbers indicate amino acid positions of each protein (D).

Figure 3. FISH analyses for PPFIBP1–ALK: sections of tumors positive for PPFIBP1–ALK were subjected to FISH analyses. In PPFIBP1–ALK fusion assays (left) the fusion genes are indicated by arrows. In ALK split assays (right) the 3’-sides of ALK are indicated by arrowheads. The color of fluorescence for the BAC clones and the case numbers in each hybridization are indicated. Nuclei are stained blue with DAPI.
formed large tumors that those expressing either PPFIBP1–ALK or EML4–ALK infected 3T3 cells into the shoulder of nude mice revealed tumor growth, which was comparable with the observation with induced hundreds of transformed foci over 14 days of culture.

Predicted molecular weight of 90,740 Da (Supplementary Fig. 1). To examine the transforming potential of PPFIBP1–ALK, a recombinant ecotropic retrovirus was generated to produce a fusion kinase of 811 amino acids with a predicted molecular weight of 90,740 Da (Supplementary Fig. 1).

Figure 4. Transforming potential of PPFIBP1–ALK. Top, mouse 3T3 fibroblasts were infected with retroviruses encoding PPFIBP1–ALK or EML4–ALK or with the corresponding empty virus (Mock). The cells were photographed after 14 days of culture. Scale bars, 400 μm. Bottom, Nude mice were injected subcutaneously with the corresponding 3T3 cells, and tumor formation was examined after 14 days. The number of tumors formed per 4 injections is indicated at the bottom.

Discussion

Since their discovery in 1994, appropriate diagnosis of ALK fusion-positive tumours with conventional anti-ALK immunohistochemistry methods has been accepted. However, EML4–ALK in lung adenocarcinoma, identified in 2007, did not stain positive for ALK with conventional immunohistochemistry methods (21, 35). We developed a sensitive immunohistochemistry method, the iAEP method, and successfully stained EML4–ALK with ordinary anti-ALK mouse immunohistochemistry method, the iAEP method, and successfully stained EML4–ALK with ordinary anti-ALK mouse monoclonal antibodies (21, 31–33). Such observation further indicates a possibility that staining cancer specimens with sensitive immunohistochemical methods (such as iAEP) may detect novel ALK fusions in the "ALK-negative" tumors defined by conventional anti-ALK immunohistochemistry methods. On the basis of this hypothesis, we have identified a novel ALK fusion in "ALK-negative" IMT.

Caution is needed in practical settings. For example, rhabdomyosarcoma, especially of the alveolar type, often expresses wild-type ALK at a detectable level with conventional anti-ALK immunohistochemistry (40). Moreover, in our experience, a small portion of small cell carcinoma and large cell endocrine carcinoma of the lung, and some sarcomas, may be positive for ALK by iAEP immunohistochemistry, expressing wild-type ALK. Therefore, in order to specifically detect ALK fusions with sensitive anti-ALK immunohistochemistry, a confirmatory test by using FISH, RT-PCR, or similar is usually required. If a tumor is positive for a confirmatory test and the suspected partner gene is not a reported one, 5'-RACE or reverse transcriptase PCR methods can be used for the identification of the suspected partner. Even if overexpressed, wild-type ALK may not be oncogenic (20, 21, 37, 38), although some investigators have suggested that wild-type ALK overexpression above a certain threshold level drives the growth of neuroblastoma (41). Further investigation will be required to clarify if wild-type ALK overexpression is a target for ALK inhibitor therapy.

IMT is a rare mesenchymal tumor that has been referred to as inflammatory pseudotumor, plasma cell granuloma, fibroxanthoma, fibrous histiocytoma, pseudosarcomatous myofibroblastic tumor, and invasive fibrous tumor of the tractheobronchial tree (42). It occurs in the soft tissues as well as in the viscera and the lung, and is more likely to occur in children and young adults. Histologically, IMT is composed of a variable admixture of bland, spindle-shaped myofibroblast-like cells and an inflammatory component of lymphocytes, eosinophils, plasma cells, and macrophages. Recent genetic studies have elucidated clonal chromosomal abnormality involving 2p23, at which ALK is located, in a subset of IMT. The expression of ALK fusion proteins is detected by anti-ALK immunohistochemistry in approximately 50% of IMT cases (42), in which various ALK fusion genes have been reported (Table 1). Collectively, these lines of evidence support ALK-positive IMT being a distinct neoplastic entity. However, the other 50% of IMT cases are negative for anti-ALK immunohistochemistry, and thus in terms of pathogenesis it remains unknown whether these ALK-negative IMTs should be included in the same entity or not. In fact, 1 ALK-negative IMT case did not respond to crizotinib therapy (29). However, we have detected a novel ALK fusion in "ALK-negative" IMT that subsequently proved positive for ALK with the iAEP immunohistochemistry method. Therefore, unexpectedly lowly expressed ALK fusions may explain the pathogenesis of a portion of "ALK-negative" IMT cases. PPFIBP1–ALK represents such an ALK fusion, although we do not yet know what proportion of "ALK-negative" IMTs can be attributed to this novel subtype. "ALK-negative" IMT warrants screening with the iAEP method to detect this fusion or other, unrecognized, ALK fusions.

PPFIBP1 codes liprin beta 1 (also called PTPRF-interacting protein-binding protein 1). This 114 kDa protein is a member of the leukocyte common antigen–related (LAR) transmembrane tyrosine phosphatase-interacting protein family that may regulate LAR protein properties via interaction with another member of the family, liprin alpha1 (43). Liprin beta 1 expresses in intestinal lymphatic endothelial cells in vitro and lymphatic vasculature in vivo,
and plays an important role in the maintenance of lymphatic vessel integrity in *Xenopus* tadpoles (44). PPFIBP1 has 5 coiled-coil domains in exons 5 through 12, and the upper 3 domains are conserved in fusion form with ALK (Fig. 2D). The coiled-coil domain is shared in all ALK fusion partners (except for NPM, MSN, and SQSTM1), with which the ALK fusion proteins homodimerize leading to constitutive activation of ALK kinase domains (8, 19). As expected, in the present study, the oncogenicity of PPFIBP1–ALK was clearly confirmed with an *in vitro* focus formation assay and an *in vivo* tumorigenicity assay.

The difference in subcellular localization has contributed to the discovery/identification of various ALK fusions. Likewise, the difference in the expression level found is here proved important in the accurate detection of fusion proteins. Sensitive immunohistochemical methods such as iAEP will broaden the potential value of immunohistochemistry, which is a simple and long-established histopathologic technique in the fields of research and diagnosis. The ALK positivity rate (approximately 50%) in IMT should be reassessed with these more sensitive methods, possibly leading to the identification of novel ALK fusions and more candidates for ALK inhibitor therapy. A novel ALK fusion, VCL–ALK, has recently been identified in renal cancers (45, 46). In addition to IMT, therefore, a reassessment of diverse "ALK-negative" human cancers may be required in the forthcoming era of ALK inhibitor therapy.

### Disclosure of Potential Conflicts of Interest

K. Takeuchi, scientific advisor for developing an anti-ALK iAEP immunohistochemistry kit (ALK Detection Kit, Nichirei Bioscience, Japan) and in charge of pathology screening for ALK fusions using the immunohistochemistry kit and an original probe set for ALK split FISH assay in a clinical trial of an ALK inhibitor (AF802, Chugai, Japan). The other authors disclosed no potential conflicts of interest.

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### Table 1. ALK fusion partners in well-documented IMT cases

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<th>Sex</th>
<th>Site</th>
<th>Year, First author</th>
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<td>M</td>
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