Oncogenic Function of a KIF5B-MET Fusion Variant in Non-Small Cell Lung Cancer

Chien-Hung Gow*,†,‡, Yi-Nan Liu†,1, Huei-Ying Li§,†, Min-Shu Hsieh§,1, Shih-Han Chang†, Sheng-Ching Luo†, Tzu-Hsiu Tsai§, Pei-Lung Chen#,‡†, Meng-Feng Tsai†† and Jin-Yuan Shih†,‡‡

*Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan; †Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan; ‡Department of Healthcare Information and Management, Ming-Chuan University, Taiwan; §Medical Microbiota Center of the First Core Laboratory, National Taiwan University College of Medicine, Taipei, Taiwan; †Department of Pathology, National Taiwan University Hospital, Taipei, Taiwan; #Graduate Institute of Medical Genomics and Proteomics, National Taiwan University College of Medicine, Taipei, Taiwan; ‡Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan; ††Department of Molecular Biotechnology, Da-Yeh University, Changhua, Taiwan; ‡‡Graduate Institute of Clinical Medicine, National Taiwan University, Taipei, Taiwan

Abstract

A kinesin family member 5b (KIF5B)-MET proto-oncogene, receptor tyrosine kinase (MET) rearrangement was reported in patients with lung adenocarcinoma but its oncogenic function was not fully evaluated. We used one-step reverse transcription-polymerase chain reaction for RNA samples to screen for the KIF5B-MET fusion in 206 lung adenocarcinoma and 28 pulmonary sarcomatoid carcinoma patients. Genomic breakpoints of KIF5B-MET were determined by targeted next-generation sequencing. Soft agar colony formation assays, proliferation assays, and a xenograft mouse model were used to investigate its oncogenic activity. In addition, specific MET inhibitors were administered to evaluate their anti-tumor activities. A KIF5B-MET fusion variant in a patient with a mixed-type adenocarcinoma and sarcomatoid tumor was identified, and another case was found in a pulmonary sarcomatoid carcinoma patient. Both cases carried the same chimeric gene, a fusion between exons 1–24 of KIF5B and exons 15–21 of MET. KIF5B-MET-overexpressing cells exhibited significantly increased proliferation and colony-forming ability. Xenograft tumors harboring the fusion gene demonstrated significantly elevated tumor growth. Ectopic expression of the fusion gene stimulated the phosphorylation of KIF5B-MET as well as downstream STAT3, AKT, and ERK1/2 signaling pathways. The MET inhibitors significantly repressed cell proliferation; phosphorylation of downstream STAT3, AKT, and ERK1/2; and xenograft tumorigenicity. In conclusion, the KIF5B-MET variant was demonstrated to have an oncogenic function in cancer cells. These findings have immediate clinical implications for the targeted therapy of subgroups of non-small cell lung cancer patients.

Neoplasia (2018) 20, 838–847

Abbreviations: ADC, adenocarcinoma; ALK, anaplastic lymphoma kinase; CT, computed tomography; HGF, hepatocyte growth factor; IHC, immunohistochemical; KIF5B, kinesin family member 5b; MET, MET proto-oncogene, receptor tyrosine kinase; NSCLC, non-small cell lung cancer; PTK, protein tyrosine kinase; RET, RET proto-oncogene; TKI, tyrosine kinase inhibitor; TTF-1, thyroid transcription factor-1.

Received 22 May 2018; Revised 26 June 2018; Accepted 26 June 2018

© 2018. Published by Elsevier Inc. on behalf of Neoplasia Press, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1476-5586

https://doi.org/10.1016/j.neo.2018.06.007
Introduction
In non-small cell lung cancer (NSCLC), a considerable proportion of patients present extensive genomic instability within their tumors. This instability occurs at different levels, ranging from simple nucleotide changes, gene amplifications, chromosomal and structural rearrangements to gains or losses of entire chromosomes [1]. Structural chromosome rearrangements have been shown to result in gene fusions and can be a major driving force for tumorigenesis [2]. Originating from chromosomal translocations, oncogenic fusion proteins are frequently observed in lung adenocarcinoma (ADC); these are typically composed of an N-terminal dimerization domain provided by the fusion partner protein fused to the kinase domain of a tyrosine kinase. These fusion proteins often lead to kinase domain activation and provide ideal targets for the development of anti-cancer therapies [3].

More than 80 chromosome rearrangements have been reported in NSCLC [4]. Anaplastic lymphoma kinase (ALK), ROS proto-oncogene tyrosine-protein kinase (ROST1) and RET proto-oncogene (RET) fusions are the most common chromosome translocations involving a kinase domain [5,6]. Kinesin family member 5b (KIF5B) is the second frequent fusion partner of ALK [4,7], and also serves as a fusion donor for RET [8]. The KIF5B gene is located on chromosome 10p11.22 and encodes the KIF5B protein. It has been suggested that KIF5B-protein tyrosine kinase (PTK) fusion proteins result in aberrant kinase activation of the PTK [6,7,9]. These fusion proteins often lead to kinase domain activation and provide ideal targets for the development of anti-cancer therapies [3].

Mapping the Translocation Breakpoint by Targeted Next Generation Sequencing
DNA was extracted from fresh frozen cell pellets using QIAamp tissue DNA extraction kits (Qiagen, Valencia, CA). Based on human genome 19, NCBI build GRCh37, 94 probes for the targeted region (32,304,368–32,306,347 in chromosome 10 for KIF5B and 116,411,501–116,415,300 in chromosome 7 for MET) and four internal controls in chromosomes 6, 10, 16, and 17 were used for targeted capture reactions. In total, 2 µg of genomic DNA was sonicated into fragment sizes of approximately 800 base pairs, and used for library construction. We next performed target enrichment using the double capture protocol (Roche NimbleGen Inc., Madison, WI) following the manufacturer’s instruction. Read sequences were analyzed using the Illumina Miseq system (Illumina, San Diego, CA) and with different tools (bwa.0.7.4, picard-tools-1.90, Genome Analysis-TK-2.5-2, and IGV2.1.16). The genomic KIF5B-MET translocation breakpoints were further confirmed by PCR using a forward primer specific for KIF5B intron 24, (5′-GGAACCTGGAAGTGAGAGTA-3′) and a reverse primer for MET intron 14 (5′-

Download Persian Version:

https://daneshyari.com/article/8456778

Daneshyari.com