**MET Exon 14 Mutation Encodes an Actionable Therapeutic Target in Lung Adenocarcinoma**

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**Abstract**

Targeting somatically activated oncogenes has revolutionized the treatment of non–small cell lung cancer (NSCLC). Mutations in the gene mesenchymal–epithelial transition (MET) near the exon 14 splice sites are recurrent in lung adenocarcinoma and cause exon skipping (METΔ14). Here, we analyzed 4,422 samples from 12 different malignancies to estimate the rate of said exon skipping. METΔ14 mutation and transcript were most common in lung adenocarcinoma. Endogenously expressed levels of METΔ14 transformed human epithelial lung cells in a hepatocyte growth factor–dependent manner. In addition, overexpression of the orthologous mouse allele induced lung adenocarcinoma in a novel, immunocompetent mouse model. Met inhibition showed clinical benefit in this model. In addition, we observed a clinical response to crizotinib in a patient with METΔ14-driven NSCLC, only to observe new missense mutations in the MET activation loop, critical for binding to crizotinib, upon clinical progression. These findings support genomically selected clinical trials directed toward METΔ14 in a fraction of NSCLC patients, confirm second-site mutations for further therapeutic targeting prior to and beyond acquired resistance, and provide an in vivo system for the study of METΔ14 in an immunocompetent host. Cancer Res; 77(16); 4498–505. ©2017 AACR.

**Introduction**

The mesenchymal–epithelial transition (MET) proto-oncogene has been extensively studied in human cancer. DNA amplification of wild-type (WT) MET, fusion of MET from chromosomal rearrangement, and activating kinase domain point mutations have all been identified as independent mechanisms of MET/hepatocyte growth factor (HGF) axis activation in cancer (1). Somatic mutations at or around the splice junctions of MET exon 14 (METΔ14) are a recurrent mechanism of MET activation and lead to a METΔ14 protein that lacks the intracellular juxtamembrane domain (2). The METΔ14 mutation and transcript occurs in around 3% to 4% of lung adenocarcinoma (LUAD; refs. 3, 4). Exon 14 of MET encodes an ubiquitin ligase site (Y1003), which promotes MET degradation (5). As such, extended protein half-life has been proposed as a selective force for METΔ14 mutations in cancer (2). Case reports have suggested varying degrees of responsiveness to experimental and FDA-approved agents that inhibit MET in patients with tumors harboring METΔ14 alleles (6), but preclinical models and clinical trials are lacking to date. Finally, acquired mutations in the MET gene have been observed recently in non–small cell lung cancer (NSCLC): one (MET<sup>E1235C</sup>) following treatment with chemotherapy, radiation and crizotinib (7), and another (MET<sup>E1227V</sup>) with an experimental MET inhibitor in an EGFR-mutant LUAD without pretreatment MET mutations (8). These reports suggest that second-site, acquired resistance might be combated by next-generation MET inhibitors. Several unanswered questions remain. Malignancies other than lung cancer have not been screened for the METΔ14 mutation and transcript. In addition, the role ligand (HGF) plays in signaling from the mutant receptor and the biochemical activity of this mutant protein has not been extensively characterized.

We describe the prevalence of METΔ14 in solid tumors and define the role of METΔ14 using both in vitro and in vivo models. We identify acquired resistance to crizotinib in a patient harboring a METΔ14 mutation. These findings qualify METΔ14 mutations as drivers of LUAD and identify a subpopulation of patients who may benefit from further development of targeted MET/HGF therapies and suggest that combinations of type I and II MET inhibitors might be best deployed together, to prevent activation loop mutations that drive single-agent resistance.

**Materials and Methods**

**mRNA expression analysis and genomic analysis**

The Cancer Genome Atlas (TCGA) PanCancer exon level RNA sequencing (RNA-seq) data were obtained (9), and mRNA data for seven types of cancers [rectum adenocarcinoma (READ), colon adenocarcinoma (COAD), lung squamous cell carcinoma...
Cell lines and cell culture

The AALE parental cell line was established and maintained as described previously (13, 14). The AALE parental cell line and the following stable cell lines were received as gifts in 2015 from P. Choi and A.H. Berger in M. Meyerson’s laboratory at Dana-Farber Cancer Institute (Boston, MA). No mycoplasma testing was performed. AALE cells were treated with 75 μg/mL cycloheximide after 5-minute exposure to HGF (50 ng/mL). Protein half-life was calculated from exponential regression of MET protein band intensity as assessed on a LiCor machine.

Trypsin assay

The experiment is a modified version of that described previously (15): intracellular (internalized) MET is protected from exogenous trypsin in cell culture while cell surface–displayed MET is trypsin sensitive (15). As schematized in Supplementary Fig. S2B, AALE cells were grown to 50% confluence and stimulated with HGF for various time periods. Subsequently, cells were shifted to 4°C, washed twice with PBS and for 10 minutes in ice-cold pH 3.7 medium (pH adjusted with HCl). After two washes with ice-cold PBS, the cells were treated with 0.1% Trypsin in PBS on ice for 30 minutes, followed by the addition of TNS (CC-5002, Lonza) and PBS washes. The cells were lysed and handled as described in the immunoblotting section in Supplementary Methods.

Results

**MET exon 14 skipping occurs in LUIAD, but rarely in other malignancies**

To determine the frequency with which MET-encoded mRNA transcripts specifically exclude exon 14 (i.e., METΔ14) in various cancer types, we examined RNA-seq from a total of 4,422 samples from the TCGA Pan-Cancer-12 set composed of cases from 12 different malignancies (9). First, we examined total mRNA expression of MET and its ligand HGF and found only LUIAD and KIRC had high levels of both transcripts (Supplementary Fig. S1A and S1B). Next, we used exon-level analysis to calculate a ratio of MET exon 14 to the average of neighboring exons 13 and 15 (r = exon 14  2/(exon13 + exon15)) (3) to identify 16 LUIAD samples from 571 (2.8% ref. 10) with METΔ14 skipping (Fig. 1A; Supplementary Fig. S1C), while the other 6 cancer types have no or low (<1.2%) rates of MET exon 14 skipping. Fourteen of 16 METΔ14 samples (87%) showed somatically encoded DNA MET alterations around splice sites (Fig. 1B; Supplementary Table S1; ref. 4). Fifteen of 2,582 samples from cancers other than lung showed RNA evidence of exon 14 skipping by the above metric. No splice site mutations supporting a somatic origin for this skipping were seen in other cancer types. Total MET and HGF mRNA expression did not differ between METΔ14 and MET wt samples (Supplementary Fig. S1D). In summary, the relatively high METΔ14 skipping rate and high total MET and HGF expression level suggest LUIAD as the appropriate setting for a deeper, functional investigation of METΔ14 function.

**MET exon 14 skipping transforms human lung epithelial cells in an HGF-dependent manner**

The majority of METΔ14 skipping occurs without MET amplification, at least in early-stage LUIAD (Supplementary Table S1; ref. 19). To model the effects of METΔ14 expression from the endogenous promoter in a lung cancer-relevant cell type, we used
CRISPR to target the MET intron/exon 14 junctions in AALE cells, an immortalized, non-transformed, human tracheobronchial epithelial cell line (14). sgRNA/CAS9-editing led to MET exon 14 skipping and METΔ14mRNA expression confirmed by RT-PCR (Supplementary Fig. S2A) and immunoblotting (Fig. 2A). Importantly, this endogenously transcribed system allowed us to decouple METΔ14’s biochemical function from overexpression, adding new knowledge to the existing ectopic expression cell line models that inevitably overexpress MET protein when introducing the mutation (4). Expression of METΔ14 from the endogenous locus (METsg) renders AALE cells anchorage independent in an HGF dose-dependent manner (Fig. 2A), despite equivalent or even lower total protein levels of the exon-skipped receptor compared to WT MET in GFPsg control AALE cells. Similarly, ectopically expressed METΔ14 cDNA transformed AALE cells in an HGF-dependent manner more efficiently than equivalently expressed wt MET under the same HGF concentration (Fig. 2B). TPR-MET, a cytosolic, hyperactive, HGF-independent MET fusion mutant with strong transforming ability (20) was used as a control for both colony formation and HGF independence (Fig. 2B). These results suggest that METΔ14 is more active than WT MET, but depends on HGF for full receptor activation and cellular transformation.

**METΔ14 increases and prolongs RAS/AKT and RAS/ERK pathway signaling**

To study the mechanism(s) underlying the transforming ability of METΔ14, we measured signaling through the MET/HGF axis to downstream effector pathways. We observed that cells with expression of METΔ14 from the endogenous locus in AALE (METsg) resulted in higher and more durable levels of phospho-Y1349 MET after HGF stimulation as compared with MET wt expressing AALE cells (Fig. 2C and D). MET/HGF signaling is known to activate Ras and its downstream PI3K–AKT and MEK–ERK pathways. AKT and MEK1/2 phosphorylation likewise increases more rapidly and persists longer after HGF stimulation (Fig. 2C), suggesting that the strength and/or duration of HGF–MET signaling is increased in cells expressing METΔ14. MET internalization/endocytosis after HGF binding plays a direct role in tumorigenesis in part because activated MET continues to signal to effectors after internalization (15). To study MET internalization, we deployed an sgRNA/CAS9-edited AALE single clone, 1F10, harboring complete (presumably biallelic) editing of MET (Fig. 2E). The addition of trypsin removes extracellular proteins and spares internalized MET, rendering it detectable by immunoblotting after cell lysis (Supplementary Fig. S2B, diagram). After HGF stimulation, METΔ14 is rapidly internalized and persists in an intercellular, active state longer than does wt MET (Fig. 2F), possibly explaining the prolonged METΔ14 signaling observed in this system.

**Loss of MET exon 14 moderately increases MET protein stability**

Deletion of exon 14 of MET prevents ubiquitination and therefore fosters stabilization of MET protein (2). We measured the half-lives of endogenously expressed wt MET and METΔ14 protein after HGF stimulation in two individual informative sgRNA/CAS9-edited AALE clones. 1F10 has complete MET editing (Fig. 2D), whereas clone 2E9 has hemizygous editing of MET (Supplementary Fig. S3A, right lane). Immunoblotting confirmed that 1F10 expresses exclusively METΔ14, whereas the 2E9 clone expresses equivalent amounts of both wt MET (upper band) and METΔ14 (lower band; Supplementary Fig. S3B). Immunoblotting of cells treated with cycloheximide and serially collected at different time points (Fig. 3A) shows that METΔ14 has a 15% longer protein half-life (t1/2; Supplementary Fig. S3C) in both homozygous clone 1F10 (7.4 hours) compared with wt parental (6.5 hours) and in hemizygous clone 2E9 (8.5 vs. 7.6 hours; Supplementary Fig. S3C). Pooled METsg cells also showed similar trends, with a METΔ14 half-life of 7.9 hours compared with the 6.2 hours for MET wt in the GFPsg pool (control; Supplementary Fig. S3D and S3E). This modest increase in t1/2 confirms the role of exon 14-encoded Cbl-binding site in MET stability, but suggests additional, negative regulatory functions possibly attributable to the exon 14–encoded domains.

**MET exon 14–encoded domains regulate MET kinase activity beyond CBL engagement**

To dissect the effects of METΔ14 on protein activity from those related to protein turnover, we generated multiple AALE cell lines with stable ectopic expression of mutant TPR-MET alleles. As TPR-MET lacks the MET exon 14 sequence (20), it has been used as a template upon which to study the independent effect(s) of exon 14 versus those of the Y1003 CBL-binding site on MET activity (21). We inserted either the wt or Y1003F exon 14 sequence into the TPR-MET fusion junction in frame with the c-terminus of MET (Fig. 3B, diagram). We generated AALE cells with stable expression...
Anchorage-independent growth was assessed by soft agar assay comparing AALE cells with stable ectopic expression of indicated constructs. Immunoblotting was determined by reverse transcription PCR from AALE parental cells and single clone (1F10) selected from MET wt and MET exon 14 was compared AALE cells targeted with GFP (GFPsg) or MET sgRNA (MET sg) under the indicated HGF concentrations. Expression of MET wt and MET sg was confirmed by immunoblotting. The sum of colonies from five random fields at week 3 is reported as the mean of duplicates (±SD). **P < 0.01.

Figure 2.

**MET Exon 14 Mutation in Lung Adenocarcinoma**

**A** Anchorage-independent growth was assessed by soft agar assay comparing AALE cells targeted with GFP (GFPsg) or MET sgRNA (MET sg) under the indicated HGF concentrations. Expression of MET wt and MET sg was confirmed by immunoblotting. The sum of colonies from five random fields at week 3 is reported as the mean of duplicates (±SD). **P < 0.01.

**B** Anchorage-independent growth was assessed by soft agar assay comparing AALE cells with stable ectopic expression of indicated constructs. Immunoblotting confirmed expression of FLAG-tagged constructs. The sum of colonies from five random fields at week 3 is reported as the mean of duplicates (±SD).

**C** AALE cell lysates were collected from GFPsg or METsg cells with HGF stimulation at the indicated concentration and time. Expression and phosphorylation of MET (pY1349), AKT (pS473), and MEK1/2 (pS217/221) were measured by immunoblotting. a-Tubulin is a loading control. Values next to each band are quantified band intensity.

**D** Ratio of phospho- to total-MET band intensity from Figure 2C at the indicated time points. MET exon 14 status (inclusion or exclusion) was determined by reverse transcription PCR from AALE parental cells and single clone (1F10) selected from MET sgRNA-targeted cells (MET sg3). **F** Trypsin assay. EGF-starved AALE cells were induced by HGF (50 ng/mL) for indicated time and then washed and cooled down on ice, followed by a treatment with trypsin for 30 minutes. Cell lysates were immunoblotted with MET and HSP90 as loading control.

of these constructs respectively confirmed by immunoblotting (Supplementary Fig. S3F). Insertion of wt exon 14 inhibits 80% of the transforming activity of TPR-MET (Fig. 3C; Supplementary Fig. S3G). Introducing Y1003F, known to prevent Cbl binding (2) in exon 14, failed to reverse the inhibition of the transforming activity of TPR-MET by wt exon 14 sequence (Fig. 3C), consistent with previous reports in mouse fibroblasts (21). Similar effects are seen on RAS-GTP loading, a marker of RAS activation (Fig. 3D). Coimmunoprecipitation of alternatively tagged proteins demonstrated that exon 14 insertion does not disrupt TPR-MET dimerization (Supplementary Fig. S3H). These results confirm the previously described inhibitory role of exon 14 (2) and suggest additional negative regulatory function(s) of the exon 14-encoded juxtamembrane domain of MET beyond prevention of CBL engagement.

**Met515 Induces LLID in a novel in vivo mouse model**

To explore the role of MET14 in vivo, we utilized a mouse lung cancer model (Fig. 4A) in which lentiviruses encoding a cDNA in cis with Cre recombinase is delivered intranasally, leading to expression of the cDNA and ablation of floxed germline elements in the same lung cancer precursor cell. As amplification of MDM2 or TP53 mutation cooccurs with the vast majority of patients with MET exon 14 mutations (4, 6), we infected immunocompetent...
Trp53<sup>fl</sup>ox mice (22) with a lentivirus encoding mouse Met lacking exon 15 (MetΔ15, the mouse equivalent of human METΔ14) in cis with Cre recombinase. Lentivirus encoding Kras<sup>G12D</sup> or GFP in cis with Cre served as controls. Mice receiving Kras<sup>G12D</sup> or MetΔ15 lentivirus became tachypneic and were euthanized at 3 months postinfection. These animals all harbored high-grade LUAD, whereas those receiving GFP<sup>+</sup>Cre virus did not (Fig. 4B; Supplementary Fig. S4A). IHC staining showed that all tumors expressed the lung marker Ttf-1 and proliferation marker Ki67 (Fig. 4C), while the MetΔ15-driven tumors specifically showed phospho-Met. Delivery of a distinct lentivirus encoding sgRNA targeting the endogenous mouse Met exon15 exon/intron junction in cis with Cre to Trp53<sup>fl</sup>ox mice resulted in adenoma but not adenocarcinoma formation at 3 months, indicating likely additive effects of MetΔ15 activity and Met overexpression or inherent differences in cDNA expression versus sgRNA editing, or both (Fig. 4C, right). In summary, the lentivirus-delivered MetΔ15 expression in combination with genetic mouse recapitulates some...
of the lung adenoma cases seen in human patients and is a model to study MetΔ15 inhibition in vivo.

Therapeutic benefit of Met inhibition in vivo

Crizotinib is FDA approved for the treatment of anaplastic lymphoma kinase (ALK)-fused NSCLC but also inhibits MET (23). Several groups have reported off-label use of crizotinib in NSCLC harboring MET exon 14 mutations (4, 19, 24). We deployed the MetΔ15/Trap53Δ expression model to study crizotinib response in vivo on MetΔ15-driven tumors. Tumor-bearing mice were randomized by tumor volume (as assessed by micro-CT performed at 8 weeks after lentiviral induction, Fig. 5A, D0 panel) to receive either crizotinib (50 mg/kg/day) or vehicle. Crizotinib-treated mice had, on average, stable disease while control animals continued to progress (Fig. 5B; Supplementary Fig. S4B). Immunohistochemistry for phospho-MET showed that crizotinib treatment inhibited Met autophosphorylation and activation (Fig. 5C). Ki-67 reactivity (Fig. 5C and D) was also significantly lower in the crizotinib-treated group. These results suggest that crizotinib has a favorable, but suboptimal, therapeutic effect in this novel Met exon skipping–driven mouse model of this important NSCLC subtype.

Response to crizotinib and acquired resistance in a patient with MET Δ14-mutated NSCLC

We found coincident METΔ14 mutation with approximately 15× amplification, among other aberrations (Fig. 5A, inserted table) in a 63-year-old, otherwise healthy, never-smoking female diagnosed with LUAD and pain. Systemic therapy with crizotinib was initiated after detection of METΔ14 mutation with approximately 15× amplification in tumor sequencing results. Restaging PET/CT demonstrated a dramatic improvement of disseminated disease involving the liver, adrenals, multiple osseous lesions, and subcutaneous disease (Fig. 6A; Supplementary Fig. S5A) and a near-complete radiographic response at 3 months (Fig. 6B). Subsequent imaging at 9 months showed progression in the liver (Fig. 6C). Cell-free DNA sequencing (18) was performed in the setting of clinical progression to explore mechanisms of acquired resistance without rebiopsy. Pretreatment MET exon 14 skipping mutation and MET amplification were identified along with four new, subclonal, missense mutations in MET: D1228N, Y1230H, Y1230S, and G1163R (amino acid numbering according to UniprotKB P08581; Fig. 6C, inserted table), all of which are located in the ATP docking pocket (25, 26) and have been previously and independently reported to activate the kinase, impair crizotinib binding (23), and to lead to resistance to other MET inhibitors in vitro (26). These mutations occur in trans from one another and in quantitatively lower allele fractions than the initial MET exon 14 mutations (Supplementary Fig. S5B), indicating convergent, acquired resistance through activation loop interactions with crizotinib. This is the first clinical documentation of multiple secondary mutations in a crizotinib-treated case of METΔ14-driven LUAD, definitively proving that METΔ14 is the target of crizotinib and that METΔ14 is a therapeutic target in LUAD.

Discussion

The need to extend targeted approaches to larger fractions of patients with cancer is clear and compelling. We find 2.8% of LUADs show evidence of MET mRNA skipping, the vast majority of which result from acquired, somatic mutations and/or deletions in or around the exon 14–coding region of the gene, detectable with genomic profiling of MET. The two of 16 samples in which we observed evidence of mRNA skipping but could not detect DNA aberrations in MET could be either false positive mRNA predictions or harbor yet unexplained mechanisms for exon 14 exclusion in the mRNA transcript of MET. The clinical relevance of this population of NSCLC is large, as METΔ14 was at least as frequent as ALK and ROS1 fusions combined in one large dataset where both fusions and skipping were evaluable (10). Our integrative genomic, biochemical, animal, and clinical analyses firmly establish METΔ14 as a driver event in NSCLC. We show that
META14 expression from the endogenous, nonamplified allele is transforming in an HGF-dependent manner, suggesting HGF levels as a possible independent determinant of activity, response, and resistance to therapy. Our experiments here were designed to decouple META14 catalytic activity from the effects of overexpression known to be transforming (27), a distinction our prior ectopic expression studies could not make (4). Our results with endogenous META14 expression levels achieved through genomic editing of a relevant human cell type argue that the exon 14-encoded portion of MET negatively regulates the kinase activity as well as the half-life of the receptor.

Case series have demonstrated variable responses to crizotinib treatment in patients with genomic MET alterations, including but not limited to META14. We show for the first time that expression of the analogous Met15 is oncogenic in adult mice and that its inhibition leads to demonstrable therapeutic benefit in vivo, proving MET itself (rather than an off-target kinase) as the most likely therapeutic target in the aforementioned clinical responses seen in patients. The use of this novel, preclinical model clarifies the likely target of a drug in routine use through directed interrogation of aberrations seen in actual patients. Variations of this flexible system could be deployed for evaluating numerous additional candidate driver oncogenes in a reliable, economically efficient, and clinically relevant timeline.

Finally, we report the first case of acquired resistance to MET inhibition through multiple secondary missense mutations clustered in the activation loop of MET. This case emphasizes several important concepts in the targeted therapy of solid tumors. Most importantly, this is the first clinical documentation of multiple secondary mutations in the META14 allele acquired upon clinical progression, definitively proving that META14 is a therapeutic target. Second, it underscores the clinical relevance of tumor heterogeneity, as evidenced by multiple missense mutations in trans to one another, converging on residues critical for crizotinib binding. Finally, this case stresses the importance of unbiased reassessment of tumor genotype at progression, which in this case nominates available MET inhibitors with distinct modes of binding for treatment of progressive disease.

Disclosure of Potential Conflicts of Interest

M. Meyerson reports receiving commercial research grants from Bayer, has ownership interest (including patents) in Foundation Medicine, and is a consultant/advisory board member for Foundation Medicine. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

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