MET in Cancer Initiation and Driver Mutations

Subjects: Others

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The *MET* gene, known as *MET* proto-oncogene receptor tyrosine kinase, was first identified to induce tumor cell migration, invasion, and proliferation/survival through canonical RAS-CDC42-PAK-Rho kinase, RAS-MAPK, PI3K-AKT-mTOR, and β-catenin signaling pathways, and its driver mutations, such as *MET* gene amplification (*MET*amp) and the exon 14 skipping alterations (*MET*ex14), activate cell transformation, cancer progression, and worse patient prognosis, principally in lung cancer through the overactivation of their own oncogenic and MET parallel signaling pathways. Because of this, *MET* driver alterations have become recognized as actionable alterations in lung adenocarcinomas since the FDA approval target therapies for *MET*amp and *MET*ex14 in 2020.

Keywords: precision medicine ; NSCLC ; target therapies ; resistance mutations ; Driver and actionable mutations

1. Introduction

The principal hallmark of tumorigenesis is cell transformation, involving the transition of normal cells into the tumorigenic state, which is characterized by the acquisition of enhanced cell proliferation and the activation of anchorage-independent growth until to form a mass, which could progress activating cell migration, the invasion of tumor cells, and finally, metastasis. However, depending on the signaling pathways altered by the driver mutations, the tumor mass would be highly proliferative, invasive, angiogenic, and or metastatic [1]. Until now, the driver mutations had demonstrated advantages favoring cell transformation, leading to tumor formation and progression. Therefore, driver statements would be evidence before testing their actionability with target drugs, which in precision medicine means that driver mutations would be recognized as predictors of therapy responses such as current actionable genes EGFR, ALK, ROS1, HER2, and MET (among others).

The *MET* gene encodes a member of the receptor tyrosine kinase (RTK) family of proteins, and, since the early 1980s, different authors have studied the effect of *MET* on cancer development, starting by Cooper et al., who were the pioneers in described *MET* gene as a “driver gene” when this concept did not exist yet, identifying it as a transforming gene detected in chemically transformed cells [2]. Afterwards, Tward et al. found that the *MET*amp would be able to induce cell transformation and hepatocellular carcinoma (HCC) in mice overexpressing a wild-type allele of human *MET*, although the carcinoma only arose in cooperation with the constitutively active β-catenin expression [3]. Perhaps this was possible through the crosstalk signaling Met/β-catenin since the inactivation of *MET* transgenes induced the regression of HCC [4]. In the same way, Mi et al., speculated whether MET could have initiated tumorigenesis in mice prostates, so they tested this idea designing a conditional Met transgenic mouse that mimicked human prostate cancer through an increased Met expression, which resulted in the oncogenic prostate transformation. Nevertheless, the presence of METamp and *PTEN* deletion leads to prostate neoplasia and prostatic adenocarcinomas, inducing an epithelial-mesenchymal transition and an increase of metastasis events [5]. As a result, METamp caused cell transformation; however, this had to take place in cooperation with another alteration in Met signaling pathways or MET parallel signaling co-activation, which could be needed to support the MET activities. All of these discoveries were the initial knowledge about *MET* in cancer; nevertheless, the development of target therapies against active MET was not initiated until the discovery of *MET*ex14, which is by far the most common driver and actionable *MET* mutation.

2. MET in Cancer Initiation and Driver Mutations

2.1. MET Amplification

In 1996, Ichimura et al. revealed that MET protein and its specific ligand, hepatocyte growth factor (HGF), were highly expressed in lung cancer cell lines, as well as in non-small cell lung cancer (NSCLC) biopsies [6][7]. However, the protein levels did not reveal whether these results were associated with a specific *MET* mutation or with the gene copy number gain (GCN) [8], which could arise from polysomy or amplification. Still, the amplification represents a biologic selection process for *MET* as an oncogenic driver. As *MET*amp has been recognized as a bad prognosis biomarker in NSCLC,

HCC, gastric cancer, and triple-negative breast cancer [9][10][11][12], its identification in precision medicine through the GCN is currently calculated using the copy number variation (CNV) from next-generation sequencing (NGS) or using the standard assay fluorescence in situ hybridization (FISH) [13].

The current *METamp* frequency in different solid cancers was estimated thanks to the AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE), which is an international pan-cancer registry [14]. According to GENIE, *MET*amp represents a 2% in non-small cell lung cancer (NSCLC 10,451 patients), a 1.2% in renal (1,556 patients), and hepatobiliary (1,854 patients) cancers, followed by a 0.4% in colorectal (7,370 patients), 0.2% in ovarian (4,481 patients), breast cancer (8,365 patients), and prostate cancers (3,530 patients). NSCLC has the highest *MET*amp and driver mutations frequency (**Table 1**), as the *MET*ex14 is the most common MET driver and actionable alteration [15][16]. Now, as much as *MET*amp and *MET*ex14 are recognized as actionable because they account for different target therapies replacing the conventional chemotherapies; despite the success in *MET*amp, the therapy response will depend on the GCN degree.

Table 1. METex14 and METamp frequency in NSCLC, renal, hepatobiliary, colorectal, ovarian, breast, and prostate cancers in the GENIE cohort [13]. Germinal mutations, uncertain significance variants, and patients missing MET analysis were filtered out using available tools at https://genie.cbioportal.org/ (last time accessed on 10 November 2022).

Cancer Type	N° GENIE Samples	N° Samples after Filters	METex14	MET Amp
NSCLC	**17,137**	**10,231**	**4%**	**2%**
Renal	**1,986**	**1,556**	**1.2%**	**1.2%**
Hepatobiliary	**2,517**	**1,854**	**0.4%**	**1.2%**
Colorectal	**11,893**	**7,370**	**0%**	**0.4%**
Ovarian	**4,606**	**4,481**	**0.1%**	**0.2%**
Breast	**13,388**	**8,365**	**0%**	**0.2%**
Prostate	**4,379**	**3,530**	**0.1%**	**0.1%**
Total analysis	**56,682**	**36,095**	**5.8%**	**5.3%**

2.2. MET Exon 14 Skipping Alterations

The *MET*ex14 was first reported in small cell lung cancer and then in NSCLC patients. Furthermore, when *MET*ex14 was expressed in normal mouse NIH3T3 fibroblasts, cells were transformed and then became tumorigenic in vivo, which confirmed *MET*ex14 as a driver alteration [17], whereas Paik and colleagues were demonstrating METex14 tumor cells were sensitive to MET tyrosine kinase inhibitors (TKIs), demostrating the clinical benefit for NSCLC patients [18].

Normally, in *MET* pre-mRNA, the introns flanking the exon 14 are spliced out, resulting in an mRNA containing exon 14, which encodes the juxtamembrane domain (JMD), which is key for MET protein degradation. The *MET*ex14 causes the loss of JMD when mutations at the splice donor or acceptor sites result in exon 14 loss, such as base substitutions, insertions, deletions, and intronic noncoding regions immediately adjacent to the splice acceptor site and the whole-exon deletion. When some of these alternatives derived in a truncated MET receptor, it shows a constitutive expression because the loss of the Tyr1003 residue located in the JMD prevents the binding of the E3 ubiquitin ligase Cbl and proteasomal degradation, which have shown overactive MET signaling pathways, triggering an exacerbate cell proliferation and invasion, contributing to the evolution of cancer and bad prognosis [19][20].

*MET*ex14 occurs in 3 to 4% of NSCLC patients (**Table 1**), and it has been identified as a potent therapeutic target encouraging the approval of TKIs [21][22]. However, the actionability of different variants which originate the *MET*ex14 alteration have not been totally validated yet. Currently, several *MET* mutations are recognized as actionable METex14 by the approved test Foundation One (such as splice site 2888-10_2911del34, splice site 2888-37_2888-30delCGTCTTA, splice site 2888-18_2888-5del14, D1010N, splice site 3028+2T>C, splice site 2999_3028+4del34, splice site 3028+1G>A, and splice site 3028_3028+2delGGT), which were searched in the GENIE public database, and, as a result, only D1010N was found, representing 9.6% of 439 *MET* driver mutations (**Figure 1** and **Table 2**). In addition, other frequent mutations recognized as a driver by GENIE impacting the exon 14 of *MET* were found, as the X1010_splice (29%), followed by the X963_splice (20.9%) and D1010H (9.7%) (**Figure 1**).

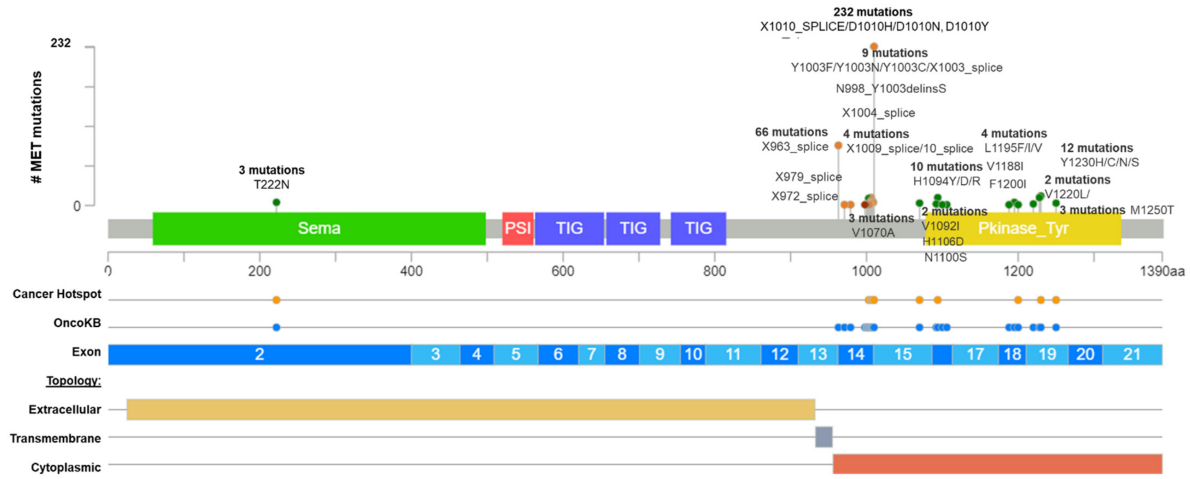

Figure 1. Common *MET* driver mutations impact principally the juxtamembrane and kinase domains (exon 14). Lolliplot of MET protein domains (Sema, PSI, TIG, juxtamembrane, and Pkinase) showing common driver mutations identified in solid tumors from **Table 1**. Additionally, the protein structure shows the cancer hotspot (yellow circle), OncoKB prediction therapies (blue circles), exons numbered (blue and light blue rectangles), and protein topology. Yellow is the extracellular region, red, the cytoplasmic region, and, gray, the transmembrane region.

After that, the researchers interrogate all these variants according to the bioinformatic driver predictors, and OncoKB as the actionability predictor, which is a precision oncology knowledge base developed at Memorial Sloan Kettering Cancer Center that contains biologic and oncogenic effects, prognostic, and predictive significance of somatic alterations [23]. As is shown in **Table 2**, sixteen alterations in exon 14 (affecting 374 patients) were recognized by different predictors, including OncoKB as oncogenic/likely oncogenic mutations with level 1 of evidence, which means these mutations concur with an FDA-approved drug. According to these results, many driver and actionable *MET* mutations had not been functionally or clinically validated yet (**Table 2**). Additionally, there is an extensive list of mutations in the *MET* hot spot between exons 14 and 19 with drugs predictions, which must be evaluated as actionable alterations (**Figure 1** and **Table 2**).

Table 2. Driver and actionable statement prediction of known MET variants. All variants showed are predicted driver and actionable. D: Deletereous, T= Tolerated

N°	Protein Change	Variant_ type	exon	CADD13	SIFT	Mut. Taster	fathm MKL	LRT	M-CAP	MetaLR	Polyphen2	driver_statement CGI	ONCOGENIC STATEMENT	ONCOKB´S EVIDENCE LEVELS
128	X1010_splice	Splice_Site	14	25.9	.	D	D	.	.	.	.	predicted driver: tier 1	Likely Oncogenic	Level 1
92	X963_splice	Splice_Site	14	42	.	D	D	.	.	.	.	predicted driver: tier 1	Likely Oncogenic	Level 1
43	D1010H	Missense	14	25	D	D	D	D	D	T	D	predicted driver: tier 1	Likely Oncogenic	Level 1
42	D1010N	Missense	14	25.9	T	D	D	D	D	T	D	predicted driver: tier 1	Likely Oncogenic	Level 1
28	D1010Y	Missense	14	28.1	D	D	D	D	D	T	D	predicted driver: tier 1	Likely Oncogenic	Level 1
8	H1094Y	Missense	16	29.0	D	D	D	D	D	T	D	known in renal_carcinoma	Oncogenic	unknown
8	X1006_splice	Frame_Shift_Del	1415	27.7	.	D	D	.	.	.	.	predicted driver: tier 1	Likely Oncogenic	Level 1
8	X1007_splice	Frame_Shift_Del	1415	31	.	D	D	.	.	.	.	predicted driver: tier 1	Likely Oncogenic	Level 1
7	Y1230H	Missense	19	48	D	D	D	D	D	D	D	known in renal_carcinoma	Oncogenic	Level R2
7	X1008_splice	Frame_Shift_Del	1415	26.7	.	D	D	.	.	.	.	predicted driver: tier 1	Likely Oncogenic	Level 1

5	D1228N	Missense	19	31	D	A	D	D	D	D	D	predicted driver: tier 1	Likely Oncogenic	Level R2
5	X1009_splice	In_Frame_ Del	1415	29.6	.	D	D	.	.	.	.	predicted driver: tier 1	Likely Oncogenic	Level 1
4	D1228H	Missense	19	27.7	D	D	D	D	D	D	D	predicted driver: tier 1	likely oncogenic	unknown
4	T222M	Missense	2	29	D	D	D	D	D	T	D	predicted passenger	Unknown	unknown
4	Y1230C	Missense	19	28.7	D	A	D	D	D	D	D	known in renal_carcinoma	Likely Oncogenic	Level 1
3	Y1003N	Missense	14	25.4	D	D	D	D	D	T	D	predicted driver: tier 1	Likely oncogenic	unknown
3	V1070A	Missense	15	32	D	D	D	D	D	D	D	predicted driver: tier 1	Likely Oncogenic	unknown
3	M1250T	Missense	19	31	D	D	D	D	D	T	D	known in: renal_carcinoma	Oncogenic	Level 1
3	Y1230N	Missense	19	26.5	D	D	D	D	D	D	D	predicted driver: tier 1	Likely Oncogenic	Level 1
3	Y1003F	Missense	14	27.7	D	D	D	D	D	T	D	predicted driver: tier 1	Oncogenic	Level 1
2	V1220L	Missense	19	27.5	D	D	D	D	D	T	D	predicted driver: tier 1	Unknown	unknown
2	V1092I	Missense	16	31	D	D	D	D	D	T	D	known in CANCER-PR;carcinoma	Oncogenic	level 1
2	D1002G	Missense	14	25.0	D	D	D	D	D	T	P	predicted driver: tier 1	Likely Oncogenic	level 1
2	Y1003C	Missense	14	28.5	D	D	D	D	D	T	D	predicted driver: tier 1	Likely Oncogenic	Level 1
2	L1195F	Missense	18	31	D	D	D	D	D	D	D	predicted driver: tier 1	Unknown	Level 1
1	H1094R	Missense	16	48	D	A	D	D	D	T	D	known in renal_carcinoma	Oncogenic	unknown
1	L1195V	Missense	18	27.7	D	D	D	D	D	D	D	predicted driver: tier 1	Oncogenic	unknown
1	V1220I	Missense	19	28.2	D	A	D	D	D	T	D	predicted driver: tier 1	Likely Oncogenic	unknown
1	Y1230S	Missense	19	26.8	D	D	D	D	D	D	D	predicted driver: tier 1	Likely Oncogenic	unknown
1	N998_Y1003delinsS	In_Frame_ Del	14	48	.	D	D	.	.	.	.	predicted driver: tier 1	Unknown	unknown
1	H1094D	Missense	16	26.8	D	D	D	D	D	D	D	predicted driver: tier 1	Unknown	unknown
1	V1188I	Missense	18	29.1	D	D	D	D	D	T	D	predicted driver: tier 1	Unknown	unknown
1	L1195I	Missense	18	48	D	D	D	D	D	D	D	predicted driver: tier 1	unknown	unknown
1	X972_splice	Frame_Shift_Del	1415	24.9	.	D	D	.	.	.	.	predicted passenger	unknown	unknown
1	X979_splice	Frame_Shift_Del	1415	29.3	.	D	D	.	.	.	.	predicted passenger	unknown	unknown
1	X1001_splice	In_Frame_Del	1415	48	.	D	D	.	.	.	.	predicted passenger	unknown	unknown

Still, the validation and approval of additional *MET* driver alterations should be the next step to offer many potentially *METex14* targetable mutations [24][25]. Indeed, a study identified five hundred genetic alterations that lead to *METex14*, and the analysis revealed that the most frequent regions impacted were the splice donor site (42%), followed by the polypyrimidine tract (15%), the splice acceptor site (~5%), and both the splice acceptor sites and the polypyrimidine tract (13%). All these alterations resulted in the elimination of exon 14 with an mRNA containing the exon 13 fused to exon 15 [26].

Thereby, given the diversity of alterations leading to *METex14* revealed in mRNA, the diagnosis sensitivity could challenge the identification of them in DNA assays. In contrast, RNA approaches directly identify 13–15 exons fusion in the transcript. For this reason, the amplicon-based approaches may fail to find *METex14* alterations because it does not allow

the detection of large deletions. However, hybrid capture is more amenable to detecting the alterations leading to *METex14*. Furthermore, this method generally isolates larger fragments of DNA, including sequences that flank the regions of interest, compared with amplicon-based methods when using DNA as the input material [27]. Additionally, 60% of positive results according to the RNA-based assay were negative using the DNA-based assay [28]. Likewise, the mRNA-based quantitative reverse transcriptase RT-PCR demonstrated 100% sensitivity in detecting METex14, compared to 61.5% sensitivity using conventional DNA-based Sanger sequencing [29], so RNA analysis seems to be best way to identify METex14 to follow with target drugs' prescriptions.

1	X1003_splice	Frame_Shift_Del	1415	48	.	D	D	.	.	.	.	predicted passenger	unknown	unknown
1	X1004_splice	Frame_Shift_Del	1415	24.9	.	D	D	.	.	.	.	predicted passenger	unknown	unknown
1	F1006_D1010delinsN	In_Frame_Del	14	48	.	D	D	.	.	.	.	predicted passenger	unknown	unknown
1	F1007_D1010delinsY	In_Frame_Del	14	48	.	D	D	.	.	.	.	predicted driver: tier 1	likely oncogenic	unknown
1	N1005S	Missense	16	48	T	N	N	N	T	T	B	predicted passenger	unknown	unknown
1	D1228V	Missense	19	26.7	D	D	D	D	D	D	D	known in LUAD	Likely oncogenic	unknown
1	H1106D	Missense	16	48	D	D	D	D	D	T	D	predicted driver: tier 1	Likely Oncogenic	Level R2
1	F1200I	Missense	18	32	D	D	D	D	D	T	D	predicted driver: tier 1	Oncogenic	Level R2
1	V1001_F1007del	In_Frame_Del	14	25.9	.	D	D	.	.	.	.	predicted driver: tier 1	Likely Oncogenic	Level 1
1	D1002_F1007del	In_Frame_Del	14	41	.	D	D	.	.	.	.	predicted driver: tier 1	Likely Oncogenic	Level 1

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