MET Exon 14 Skipping Analogs: Rare but Potentially Clinically Actionable

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Background

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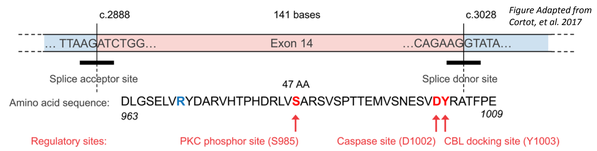
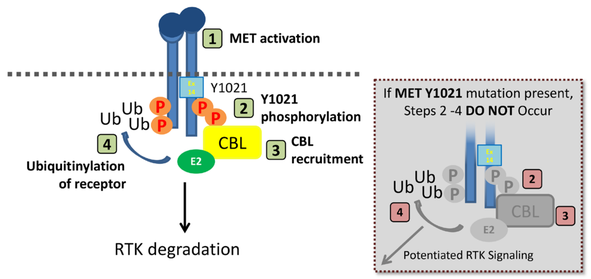
The DpY motif within the exon 14 juxta-membrane domain of the MET receptor gene is a critical regulatory site on the MET gene, specifically, where Cbl docks to mediate negative regulation. Splicing alterations that delete this residue, known as exon 14 skipping mutations (ex14sk mt), lead to prolonged MET protein stability and oncogenic signaling. Specific mt at the Y1021 (aka 1003) residue (actual Cbl docking site) are thought to lead to similar effects as ex14sk, but due to their rarity, their role in NSCLC is unknown.

Figure 1. MET regulation mediated by Y1021 Cbl-Binding Site





Study Objectives

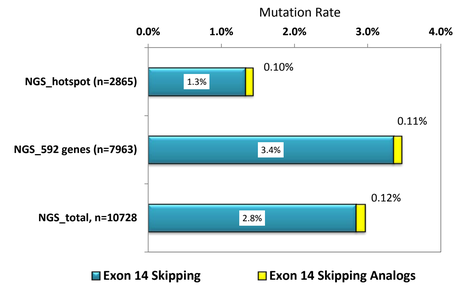
Determine the (1) rate, (2) co-occurring alterations, (3) protein expression pattern, and (4) clinicopathological patterns of ex14sk analog and compare with ex14sk.

Methods

Retrospective review of molecular profiles for non-ex14sk mt that include/surround the DpY motif (Y1021) in MET. Numbers updated since ASCO abstract submision. Two NGS platforms were included: MiSeq (2014-2017; n = 2865) and NextSeq (2017-2019; n = 7963). Immunohistochemistry (IHC) of cMET (SP44) and co-occurring alterations (EGFR, KRAS, ALK, ROS, etc.) were also reviewed.

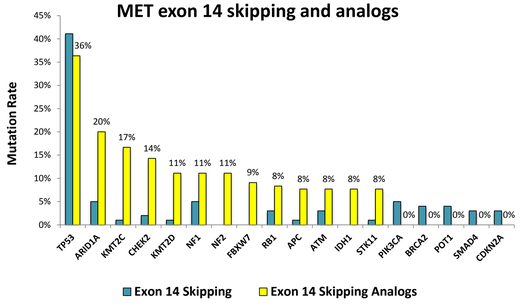
Results

Figure 2– MET exon 14 skipping and analog rates in NSCLC



MET exon 14 skipping analog mutations are rare events, occurring at a frequency of 0.12% (13/10,728), compared to MET exon 14 skipping which occur at a frequency of 2.8% (305/10,728).

Figure 3– Co-occurring mutations in MET exon 14 skipping and analogs



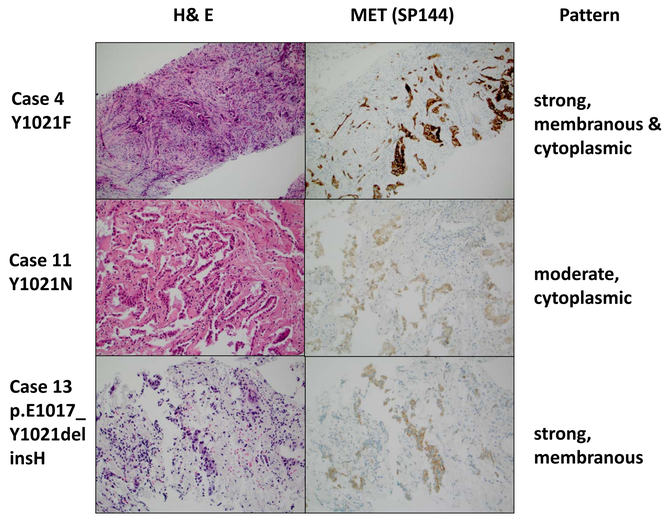
MET exon 14 skipping and exon 14 skipping analog mutants exhibit 30-40% TP53 co-mutations, but differences were observed for the remaining co-mutated genes.

Table 1. Clinicopathological, Co-Mutation and Expression Features of MET Exon 14 Skipping Analogs

Case	Smoking Hx	Gender	Age	Histology	Stage	protein change	MET IHC	MET CN	Staining Pattern	Driver Status
1	n/a	M	82	adenocarcinoma		p.Y1021F	2+ 90%	4.4		neg
2	Former smoker	F	84	adenocarcinoma	III	p.Y1021F	2+ 10%	1.7		neg
3	n/a	F	85	adenocarcinoma	IV	p.Y1021F	n/a	5.5		neg
4	n/a	F	80	adenocarcinoma	IV	p.Y1021F	3+ 100%	3	membranous/cytoplasmic	neg
5	n/a	M	83	Invasive sarcomatoid	IV	p.Y1021F	2+ 100%	1.5	membranous/cytoplasmic	neg
6	n/a	F	71	adenocarcinoma		p.Y1021H	2+ 5%	2.25		neg
7	n/a	F	77	adenocarcinoma		p.Y1021H	3+ 100%	na		neg
8	Former smoker	M	79	mixed; squamous/ adenocarcinoma	IV	p.Y1021H	3+ 100%	7.5	memranous	neg
9	Former smoker	M	81	adenocarcinoma	IV	p.Y1021H	n/a	na		neg
10	Former smoker	M	83	adenocarcinoma	IV	p.Y1021N	3+ 100%	3		neg
11	Former smoker	F	69	adenocarcinoma	IB	p.Y1021N	1+ 100%	0.98	cytoplasmic	neg
12	n/a	F	71	adenocarcinoma	IV	p.Y1021C	n/a	2.24		neg
13	Never smoker	F	84	adenocarcinoma		p.E1017_Y1021delinsH	2+ 80%	1.47	membranous	neg

Thirteen patients with exon 14 skipping analog mutations were assessed for clinicopathological features, and if available, examined for MET protein expression. Median age was 81, 62% (8/13) were female, most were adenocarcinomas and biopsies were obtained from tumors at different stages. Different levels of expression were observed, but most exhibited moderate to strong expression levels of cMET protein.

Figure 4– Different MET staining patterns in MET exon 14 skipping analogs



Photomicrographs for three cases demonstrating variations in MET expression patterns. Case 4 and 11 are substitutions at the Y1021 codon, whereas Case 13 harbors a small deletion insertion extending a few of codons upstream of Y1021.

Conclusions

- MET exon 14 analog mutations are rare events occurring at a frequency of 0.1%
- Similar to patients with exon 14 skipping mutations, substitutions and small indels at Y1021 exhibit Clinicopathological features such as previous smoking history and older age, mutual exclusivity with oncogene drivers and MET protein overexpression
- The rarity of these analogous exon 14 skipping mutations suggests deletions of exon 14 provide cellular advantages beyond Cbl-mediated ubiquitinylation of MET.
- Although rare, the impact of these mutations on efficacy of Met-directed therapy deserves further exploration.
- Further studies comparing MET exon 14 skipping mutants, analogs and other exon 14 mutants may provide more insight into the underlying biology and contribution of additional regulatory sites upstream of Y1021, including the PKC phosphorylation site and Caspase cleavage sites

References

1. Cortot, A.B., D. Tulasne, et al. (2017). "Exon 14 Deleted MET Receptor as a New Biomarker and Target in Cancers." J Natl Cancer Inst 109(5):djw262
2. Awad, M. M., L. Sholl, et al. (2016). "MET Exon 14 Mutations in Non–Small-Cell Lung Cancer Are Associated With Advanced Age and Stage-Dependent MET Genomic Amplification and c-Met Overexpression." J Clin Oncol 34: 721-730.