Title: Comparative genomic analysis reveals distinctive immune profiles in MET exon 14 mutated and MET amplified lung cancer

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Scientific Abstract:

Background: In non-small cell lung cancer (NSCLC), the MET tyrosine kinase receptor can be mutated or amplified resulting in dysregulation of receptor function leading to tumor proliferation. MET exon 14 (METEx14) mutated and MET amplified NSCLC tumors have shown varied response to immunotherapy. Therefore, we sought to compare the genomic and immune landscape of MET-altered NSCLC.

Methods: The genomic profiles of 3,821 NSCLC tumors sequenced using the Strata Select assay on the Strata Oncology Platform were analyzed. Tumors were sorted based on METex14 mutations, MET amplification (METamp) defined as copy number gain (CNG) ≥6 and MET wild-type (METwt). The RNA expression of 19 immune regulatory genes, tumor mutation burden (TMB), Strata Immunotherapy Response Signature (IRS) score and the frequency of gene co-alterations were compared across groups. Statistical comparisons of medians were done with Kruskal-Wallis testing and categorical comparisons with Chi square using R Studio version 4.3.2.

Results: 122 (3.2%) METex14, 70 (1.8%) METamp, and 3,629 (95.0%) METwt were identified. Patients with METex14 were older and more frequently female. MET gene expression was found to be higher in METamp (median 14.4) compared to METex14 (median 12.3) ($P<0.01$). TMB was lowest in METex14 (median 2.7) group compared to METamp (median 7.1) and METwt (median 5.1) ($P<0.001$). High PD-L1 expression occurred in 71.4% of METamp, 68.0% of METex14 and 41.3% of METwt ($P<0.001$). Overall, METamp tumors had a greater proportion of high IRS scores (52.9%) compared to METex14 (35.2%) and METwt (45.4%) ($P<0.01$). mRNA expression of immune checkpoints CTLA4, PD-1, LAG3, IDO1, TIGIT and HAVCR2 were all higher in METex14 compared to METamp and METwt ($P<0.001$ for all). METex14 tumors also exhibited higher gene expression of CD4, CD8A and FOXP3 compared to METamp and METwt ($p<0.001$). METex14 had higher prevalence of MDM2 amplification (34% vs 3% vs 4%) and lower prevalence of alterations in EGFR (0.8% vs 22% vs 21%), KRAS (0.8% vs 10% vs 26%), CDKN2A (17% vs 29% v 28%) and TP53 (34% vs 87% vs 64%) compared with METamp and METwt tumors, respectively ($p<0.05$).

Conclusion: METex14 and METamp tumors harbor distinct immune-gene expression profiles and co-occurring gene alterations that distinguish themselves from each other and METwt tumors. Further analysis must be conducted to determine how these variations impact immunotherapy in MET-altered NSCLC.

Written Lay Abstract:

A gene in our DNA called MET makes proteins that help send signals in cells and helps with healthy cell growth and survival. When this MET gene is mutated (changed), cancer cells can grow and spread in the body.

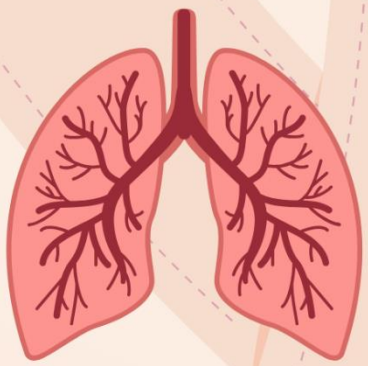
Mutations in the MET gene can lead to a type of lung cancer, called non-small cell lung cancer (NSCLC). One mutation, called MET amplified (METamp), leads to more copies of the gene, and increases the growth of cancer. Another mutation, called MET exon 14 skipping mutation (METex14), causes the part of the gene that turns cell growth off to be removed (skipped) and results in more cell growth that can spread cancer.

In this study, scientists looked at the DNA of lung tumors with MET gene mutations. They found that tumors with the METamp and METex14 gene mutations had different immune profiles. An immune profile helps predict how well immunotherapy (a cancer treatment) will work in a patient. So, lung cancer tumors with these different mutations may be better treated by unique cancer treatments. Future studies on how the mutations affect immune profiles will help us understand how to better treat lung cancers caused by MET gene mutations.

Visual Lay Abstract:

How can we better treat lung cancer?

Our DNA has a gene called MET that helps cells stay healthy and grow normally. When MET is mutated, cancer can grow and spread.



Scientists found that lung cancer tumors with different MET gene mutations may need different cancer treatments.

Future studies can look at what cancer treatments may work best for lung cancers with different MET mutations. This research helps us know how to better treat lung cancer.

Poster abstract from Javeri et al. AACR 2024:

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