Study discloses clinical-relevant intertumoral heterogeneity of NSCLCs driven by MET exon 14 skipping

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A study presented today at the IASLC World Conference on Lung Cancer 2022 in Vienna disclosed the clinical-relevant intertumoral heterogeneity of non-small cell lung cancer (NSCLC) driven by MET exon 14 skipping.

MET exon 14 skipping, as a rare driver for non-small cell lung cancer (NSCLC), can be successfully targeted by MET specific tyrosine kinase inhibitors (TKI) like savolitinib, tepotinib, and capmatinib. Recent clinical trials of MET selective TKIs displayed encouraging clinical efficacy but nearly half of NSCLC patients with MET exon 14 skipping did not benefit from MET-TKI treatment, which indicated biological heterogeneity in NSCLCs driven by METex14 skipping.

To examine this further, Dr. Yuchen Han, Shanghai Chest Hospital, China, aimed to disclose the intertumoral heterogeneity of METex14 skipping positive NSCLCs at the functional level.

To accomplish this, Dr. Han and her colleagues examined 126 formalin fixed, paraffin embedded specimens from NSCLC patients with METex14 skipping from the Department of Pathology at Shanghai Chest Hospital from April 2017 to December 2020. All samples were subjected to targeted RNA sequencing using a panel consisting of 2660 onco-immunology genes. Functional enrichment of each sample was evaluated by single sample Gene Set Enrichment Analysis (ssGSEA) and

pathway-level unsupervised clustering was conducted to identify molecular subtypes in METex14 skipping positive patients. Subtype-specific pathways, tumor microenvironment, and clinic-pathological features were further analyzed.

Four molecular subtypes were established, including subtype A (33.3%), subtype B (15.1%), subtype C (14.3%), and subtype D (37.3%).

- Subtype A was significantly associated with more aggressive clinical characteristics (more advanced stage, larger tumor size, and higher percentage of invasive morphology) and numerically shorter disease-free survival (P=0.057). Subtype A was characterized as activation of MET signaling and immune-suppressive microenvironment, such as up-regulation of PTK2, cell motility, glycolysis, hypoxia, and epithelial and mesenchymal transition (EMT), higher infiltration of Treg cells.
- Subtype B was associated with Fatty acid metabolism as well as response to oxidative stress.
- Subtype C was categorized as immune activation phenotype which also displayed higher infiltration of Tcells and macrophages as well as a higher level of MHC II signatures.
- Subtype D displayed "bypass" activation of oncogenic pathways like WNT, MAPK, NOTCH, and ERBB signaling pathways.

"This study disclosed the clinical-relevant intertumoral heterogeneity of NSCLCs driven by MET exon 14 skipping. Based on the molecular subtyping, subtype A was more sensitive to MET-TKIs, while subtype D was putatively resistant to MET-TKIs," said Dr. Han. "Of note, subtype C might be more vulnerable to immunotherapy."

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