MET Inhibitor is Expected to Overcome MET Amplification-Induced Immunotherapy Resistance in Non-Small Cell Lung Cancer

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In 2018, lung cancer occurred in 2.09 million people and resulted in 1.76 million deaths worldwide.\(^1,2\) It imposes a great disease burden on patients in China with a rapidly increasing trend during the past decades.\(^3,4\) Non-small cell lung cancer (NSCLC) is the main subtype of lung cancer, representing 80%–85% of all lung cancer cases. With impressive clinical activity, immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1), and PD-ligand 1 (PD-L1) have changed the treatment paradigm of NSCLC.\(^5\) However, not all NSCLC patients can show a response to ICIs.\(^5-7\) Recent studies have shown that some canonical driver gene alterations such as epidermal growth factor receptor (EGFR)-mutations and serine/threonine kinase 11-mutation together with KRAS-mutation, could actually speed the development of ICI-resistance in NSCLC, even though these tumors always have high PD-L1 expression.\(^7,8\) Therefore, there is an urgent need to better understand the mechanisms for immunotherapy response and identify the relevant biomarkers.

Hepatocyte growth factor receptor (MET) encodes a transmembrane glycoprotein cell surface receptor with tyrosine kinase activity that plays a critical role in organ formation and embryonic development. It is one of the important oncogenic driver genes of NSCLC. Activated MET can mediate primary and/or secondary resistance to EGFR-tyrosine kinase inhibitors (TKIs) in NSCLC,\(^9\) but the role of MET in regulating the antitumor immune response remains unknown. Better understanding the alterations of MET gene and their interaction with tumor immune microenvironment is very important for the treatment of NSCLC patients with primary MET amplification or EGFR-TKI-resistance.

In a study recently published in Cancer Discovery, titled “MET amplification attenuates lung tumor response to immunotherapy by inhibiting STING”, Zhang et al.\(^{10}\) enrolled and examined 81 NSCLC patients treated with ICI to explore the MET amplification-associated molecular mechanism in ICI resistance. They found that NSCLC patients with MET amplification not only had poor progression-free survival but were also resistant to ICI. In addition, the expression level of stimulator of interferon gene (STING) and the infiltration of antitumor T-cells were significantly decreased in NSCLC tissues with MET amplification. Single-cell RNA sequencing (scRNA-seq) was further performed to analyze more than 20,000 immune cells in NSCLC. Based on the data of scRNA-seq, the authors identified an immunosuppressive signature of decreased CD8\(^+\) T-cell and natural killer (NK) cell populations and increased XIST\(^+\) CD96\(^+\) exhausted NK cell population in NSCLC patients with MET amplification. In the mechanistic study, they found that...
MET could induce up-frameshift suppressor 1 (UPF1) phosphorylation, and the phosphorylated UPF1 could inhibit the expression of STING by changing the length of its three prime untranslated region (3'-UTR). Moreover, MET amplification-induced ICI resistance could be overcome by MET inhibition.

This study indicated that MET amplification could suppress the response of interferons and the infiltration of CD8+ T-cells and NK cells into tumor tissues by inhibiting the expression of STING and thereby leading to reduced tumor immunogenicity, and resistance to ICI. All of the above changes could be reversed by MET inhibitors. Therefore, it is theoretically feasible to overcome the resistance of MET-amplified NSCLC to immunotherapy by combining MET inhibitor and ICI. As we know, enhancing the inflammatory response in tumor microenvironments such as increasing the infiltration and activity of T-cells and NK cells and the immunogenicity of tumor cells are the most important strategies for immunotherapy. Recent studies have reported that STING agonists had antitumor effects. It mainly enhances NK cell activation and cytotoxicity by increasing interferon expression and then creates an antitumor immune microenvironment.\[11,12\]

The present study proved the negative correlation between MET amplification and STING expression in NSCLC. This study demonstrated that MET amplification in NSCLC was associated with the inhibition of STING. This finding provided a theoretical basis for reversing immunotherapy resistance through MET inhibitors. UPF1 is a kind of multifunctional RNA helicase and part of the exon junction complex. It mainly involves in nonsense-mediated mRNA decay, which is an mRNA quality-control mechanism that eliminates mRNAs containing premature stop codon.\[13,14\] Indeed, the previous study found that it could sense the length of 3'-UTR to promote mRNA decay.\[15\]

The present study confirmed this finding. It showed that MET suppressed STING mRNA surveillance through phosphorylation of UPF1 at Y818.

In this study, the authors identified MET amplification as an essential biomarker for predicting ICI resistance in NSCLC patients. Moreover, they reported the underlying molecular mechanisms of MET amplification involved in ICI resistance for the first time. This valuable information suggests that the combination of MET inhibitors and ICI can overcome ICI resistance caused by MET amplification in NSCLC. This should be further tested in a well-designed prospective clinical trial.

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Conflicts of interest
There are no conflicts of interest.

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