Correlation Between MET Gene Amplification and TP53 Mutation in Upreregulating PD-L1 Expression in EGFR-Wild-Type Lung Cancer

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Background

- The programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) signaling axis plays a critical role in tumor immunity evasion.
- PD-1 blockade can be achieved through the use of anti-PD-1 agents, notably nivolumab and pembrolizumab.
- For both agents, higher levels of PD-L1 expression can be associated with increased response to therapy, although patients with lower PD-L1 expression levels can derive clinical benefit.
- Nivolumab and pembrolizumab are antibodies that target PD-1 and showed success in treating some types of cancers. Nivolumab and pembrolizumab are approved in the US and EU for the treatment of specific stages and specific conditions of certain tumors including melanomas, NSCLC, advanced renal cell carcinoma, Hodgkin lymphoma, recurrent/metastatic SCCHN (in the US only), and locally advanced/metastatic urothelial carcinoma (in the US only).
- PD-L1 assessment by IHC is frequently used for predicting response to immunotherapy with anti-PD-1. However, the correlation between PD-L1 expression and response to immunotherapy remains poor and the search for better predictors of response continues, especially for combination therapy.
- EGFR mutations are common in NSCLC, but the majority of patients with NSCLC and EGFR mutations develop resistance to EGFR kinase inhibitors. Acquiring mutations in T790 and exon 20 has been reported as a cause for resistance, but the most common cause involves activation of additional signaling pathways, including MET amplification, HER2 amplification, KRAS mutation, and BRAF mutation. MET gene activation by amplification has been reported to be associated with resistance to EGFR inhibitors.
- Our prior studies showed a correlation between TP53 mutation and PD-L1 expression in NSCLC.

Objective

Evaluate the relative correlation between the levels of PD-L1 expression with MET gene amplification and EGFR, KRAS, or TP53 mutations in non-small-cell lung cancers.

Methods

- Tissue samples collected from 397 core biopsies or resections from lung cancers were studied for MET gene amplification by fluorescent in-situ hybridization (FISH) using MET (7q31) probe and centromere 7 probe as a control. Signals were quantified and altered ratios were calculated.
- PD-L1 expression on the same samples was evaluated using clone SP142 and standard immunohistochemistry (IHC) procedures. Biopsies were reviewed and scored by trained/certified pathologists at NeoGenomics Laboratories using NGS.
- Samples were also sequenced using next generation sequencing (NGS) for mutations in TP53, KRAS, and EGFR.
- Standard statistical tests evaluated correlations between variables including: Fisher's exact, Chi-square, Wilcoxon rank sum test Mann-Whitney U test, Spearman correlation, Pearson correlation, and the Kruskal-Wallis test.

Result

- 166 of 397 (42%) lung cancers expressed various levels of PD-L1.
- Of the 397 patients, various levels of PD-L1 were expressed in 166 (42%) between 1% and 50%, and 23 patients (7%) had expression in 1% to less than 1% of tumor cells.
- Of the 397 patients, various levels of PD-L1 were observed in 166 (42%) between 1% and 50%, and 27 patients (7%) had expression in 1% to less than 1% of tumor cells.
- There was significant correlation between TP53 mutation and overall PD-L1 expression (P=0.0001) when PD-L1 expression was considered as a continuous variable.
- Positive correlation between TP53 mutation and PD-L1 expression was observed in 87% of patients.

Conclusions

- MET gene amplification is correlated with higher expression of PD-L1.
- EGFR-mutant lung cancers have significantly lower expression of PD-L1 when clone SP142 and NGS for detecting EGFR mutations are used, but tumors without EGFR mutation have higher levels of PD-L1. MET, PD-L1, and mutation.
- Patients with TP53 mutation had strikingly high expression of PD-L1 using the SP142 clone and higher copy numbers of the MET gene.
- These data suggest that in lung cancer, both MET and TP53 genes play a direct role in up-regulating PD-L1 expression.
- Combination therapy targeting MET and/or TP53 along with immunotherapy should be considered as treating NSCLC that is EGFR-negative, especially when TP53 is mutated or MET is amplified.