Characterization of Tumor Mutation Load (TML) in Solid Tumors

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Abstract

Background: Rapid advances in immunotherapy have created a need for biomarkers to improve patient treatment selection. TML is proposed as a predictor of tumor immunogenicity due to its association with tumor immunogenicity.

Methods: TML was assessed in 7,748 solid tumors from 14 different cancers using somatic nonsynonymous missense mutations sequenced with a 592-gene panel. High TML was set at ≥ 17 mutations per megabase (mt/MB) based on an established concordance (>99%) with MSI-high status in colorectal cancer (CRC).

Results: Mean TML was highest in melanoma (Mel, 21 mt/MB), non-small cell lung cancer (NSCLC, 11 mt/MB), and bladder cancer (BLC, 11 mt/MB), whereas prostate cancer (PC), pancreas adenocarcinoma (PA), and renal cell carcinoma (RCC) had the lowest levels (all 6 mt/MB). High TML was seen most frequently in Mel (58%), NSCLC (31%), BLC (31%), and anal cancer (SCCA, 19%), whereas it was seen least frequently in PA (16%) and RCC (3%). Primary NSCLC carried lower TML than its brain metastases (13 vs. 16 mt/MB, p < 0.001). Older age was associated with higher TML in Mel (p = 0.001), CRC (p < 0.001), breast cancer (BC, p = 0.01), and NSCLC (p < 0.001). Presence of mutations in oncogenic driver genes such as EGFR, ALK, ROS1, and RET fusions, as well as V600E and KRAS mutations in Mel (17 vs. 26, p = 0.003). Conversely, mutations in tumor suppressor genes such as ARID1A (CRC, NSCLC, and BLC) and NF1 (BC, CRC, Mel, and RCC) were associated with higher TML (p < 0.05). MSI-high was correlated with high TML in CRC and gastric cancer (p < 0.05). The horizontal red line within each read box represents the median value and the bottom and top of each box represents the median value and the bottom and top values. The green lines indicate the average TML.

Results, continued

Conclusions: TML varied significantly among different cancers. High TML was associated with older age, presence of tumor suppressor gene mutations, and absence of other oncogenic mutations. Future studies will assess the impact of TML on clinical outcome and establish the role of TML in selecting patients for immunotherapy.

Methods

TML was assessed in 7,748 solid tumors from 14 different cancers using somatic nonsynonymous missense mutations sequenced with a 592-gene panel.

High TML was set at ≥ 17 mutations per megabase (mt/MB) based on an established concordance (>99%) with MSI-high status in CRC.

Primary antibodies used for PD-L1 analysis were SP142 (non-NSCLC) and 28-8 (NSCLC).

Universal cutoff of 2+ was used as the cutoff.

PD-L1 expression on the membrane of tumor cells was evaluated.

Results

Figure 1: Landscape of tumor mutational load across 14 cancer types. Top: TML-high was defined as TML ≥ 17 mutations/megabase. Bottom: The green lines indicate the average TML.

Percent of TML-High in 14 cancer types

Figure 2: The proportion of samples that are TML-high and/or PD-L1-high.

Results, continued

Conclusions

TML, assessed by NextGen sequencing on a 592-gene panel, revealed significant variation among different cancers.

Assessment of both TML and PD-L1 may identify potential responders to immune checkpoint inhibitors.

Cancer types that carry the highest proportion of favorable molecular profile to immune checkpoint inhibitors include melanoma, bladder cancer, anal cancer, NSCLC, kidney cancer and small bowel adenocarcinoma.

Overall, male gender is associated with high TML, likely due to etiological factors including UV, smoking and viral infection.

In addition to a known correlation with MSI-H, high TML was associated with older age, presence of tumor suppressor gene mutations, and an absence of other oncogenic mutations.

Future studies will assess the impact of TML on clinical outcome and establish its role in selecting patients for immunotherapy.

References