

INTEGRATION OF MULTIPLE IMMUNE-ASSOCIATED BIOMARKERS FACILITATES CLASSIFICATION OF SOLID TUMORS BY PRIMARY IMMUNE ESCAPE MODE AND PREDICTION OF PATIENT OUTCOMES

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Background Many individual biomarkers describe the idiosyncrasies of each tumor and its interactions with the tumor microenvironment (TME). However, tumors often evade immunotherapy through multiple immune escape mechanisms. Here, we present a method of integrating immune and neoplastic biomarkers that classify tumor and immune activity in the TME.

Methods Standard-of-care comprehensive genomic and immune profiling was performed on 5450 FFPE tumors representing 39 histologic types, assessing expression levels of 395 immune genes and >500 tumor-associated genes. From this data, three previously published gene expression signatures were calculated: cell proliferation (CP), tumor immunogenic signature (TIGS), and cancer testis antigen burden (CTAB). PD-L1 status of each tumor was assessed by IHC, and tumor mutational burden (TMB) was calculated. Principle component analysis (PCA) and unsupervised clustering revealed four distinct biological groups. Subsequently, a nearest neighbor method was used to classify an immune checkpoint inhibitor (ICI) treated 242-patient validation cohort (Lung cancer, melanoma and renal cell carcinoma) into these groups, the association between these groups and ICI treatment response was determined by overrepresentation analysis, and overall survival was assessed using Kaplan-Meier and CoxPH analyses.

Results PCA and clustering generated four groups: 1) Tumor-dominant, exhibiting high CTAB, TMB, and CP, and low PD-L1 and TIGS; 2) Proliferative, exhibiting high CP and low TIGS, PD-L1, CTAB, and TMB; 3) Inflamed, exhibiting high TIGS and low CP, PD-L1, CTAB, and TMB; and 4) Checkpoint, exhibiting high PD-L1, TIGS, and TMB, and low CTAB. Classifying the validation cohort into these groups, significant association with ICI response was found, with the checkpoint group overrepresented by the highest proportion of disease control [$p=0.0313$]. Kaplan-Meier survival analysis suggested a significant relationship between these groups and overall survival [$p=0.035$], with the proliferative and checkpoint groups demonstrating increased survival over tumor-dominant and inflamed groups. CoxPH analysis showed the checkpoint group to have a significantly decreased hazard ratio [HR=0.28; $p=0.024$] for ICI treatment. In all Kaplan-Meier and CoxPH analyses, this approach outperformed any of its constituent biomarkers as a survival predictor.

Conclusions Our study demonstrated that an integrated approach combining comprehensive tumor profiling and emerging biomarkers better predicts ICI response and survival in multiple histologies. Divergent outcomes between the resulting groups are likely the result of distinct tumor-immune interaction modalities. As we further validate this methodology, we hope to produce a treatment decision and clinical trial selection tool leveraging tumor-immune interactions in solid tumors to outperform single marker testing.

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