Cancer testis antigen burden: pan-cancer distribution and survival implications

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Purpose of Study

Cancer testis antigens (CTA) are highly immunogenic genes with the ability to cause cancer-specific immune responses when expressed. Their tumor cell-specific expression makes them a key target of natural T cell response, cancer vaccines, immune checkpoint blockade (ICB), and cell-based immunotherapies in a wide range of tumor types. In this study, we assess the pan-cancer distribution and ICB survival association of CTA burden (CTAB) in real-world solid tumors.

Procedure

- Three tumor sample cohorts were studied:
  1. A pan-cancer discovery cohort to develop a low- and high-CTAB cutoff (n=5450, 39 tumor types) [1]
  2. A TCGA cohort (n=19923, 32 tumor types) used to validate the classifier based on CTAB distribution and serve as a non-ICB-treated population [2]
  3. An ICB-treated retrospective cohort to validate the classification on overall survival (OS) (n=242, 3 tumor types) [3]
- The expression levels of 17 CTA were measured using targeted RNA-Seq of FFPE tumor samples and then ranked against a pan-cancer reference population (Figure 1).
- CTAB was calculated for each sample, cohort and tumor type as the sum of the 17 CTA gene expression ranks.
- The discovery cohort median CTAB of 171 was used to classify all three cohorts into high- and low-CTAB groups.
- OS analysis was performed on the TCGA and ICB-treated cohorts using a CoxPH regression model to determine the Hazard Ratio (HR).

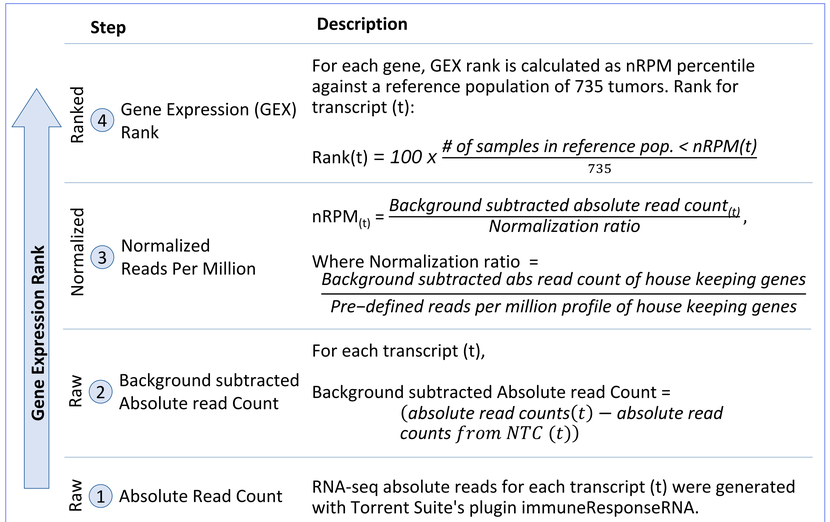

Figure 1: Flow chart showing calculation of gene expression normalized reads per million (nRPM) from raw absolute read count values in the discovery cohort [1].

Results

Table 1: Cohort CTAB composition.

Cohort	N	Median CTAB	N Positive (CTAB≥171)	N Negative (CTAB<171)
Discovery	5634	170	2806	2828
TCGA	19923	254	6413	2860
Retrospective	242	256	148	94

The three cohorts demonstrated overlapping single-peak, left-skewed CTAB distribution curves (Figure 2) centered at CTAB values between 170 (discovery cohort) and 256 (retrospective cohort).

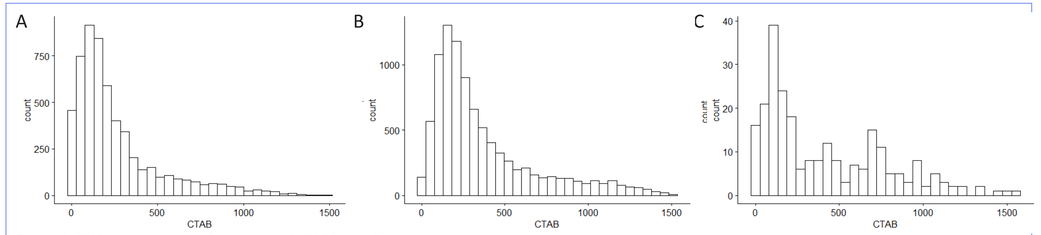

Figure 2: CTAB distributions in A) discovery, B) TCGA, and C) retrospective cohorts.

When grouping by tumor types and ordering by median CTAB, the CTAB distributions for tumor types within all three cohorts were comparable (Figure 3).

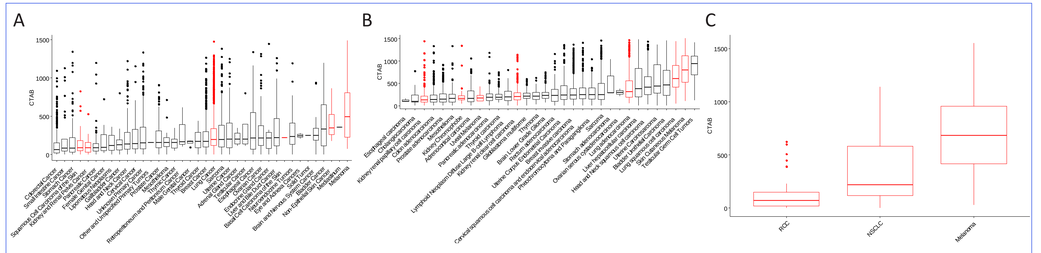

Figure 3: Cancer type CTAB distributions in A) discovery, B) TCGA, and C) retrospective cohorts

CoxPH regression analysis revealed an association between the CTAB threshold classifier and OS in both the ICB-treated retrospective and non-ICB TCGA cohorts (Figure 4). However, the direction of this association differed between the two cohorts, with high-CTAB samples having better survival (HR=0.936, p=0.076) in the ICB-treated retrospective cohort and worse survival (HR: 1.007, p=0.084) in the non-ICB-treated cohort.

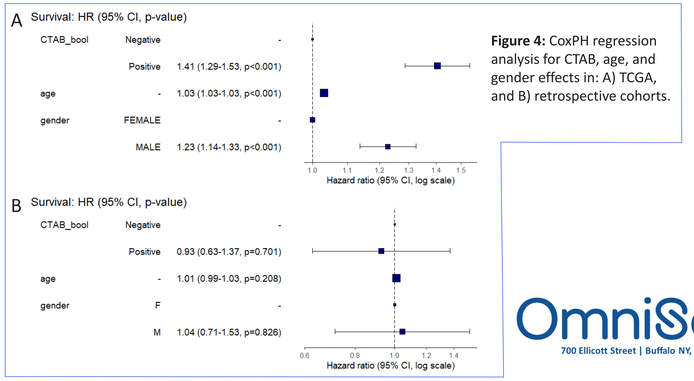

Figure 4: CoxPH regression analysis for CTAB, age, and gender effects in: A) TCGA, and B) retrospective cohorts.

Kaplan-Meier survival analysis revealed a strong association (p<0.000) between positive CTAB status and worse survival in the TCGA cohort (Figure 5). This association did not exist in the retrospective cohort (p=0.64), though positive CTAB status trended toward better survival. This difference suggests that advances in immunotherapy targeting CTA have largely eliminated the survival disbenefit observed in the pre-immunotherapy TCGA cohort.

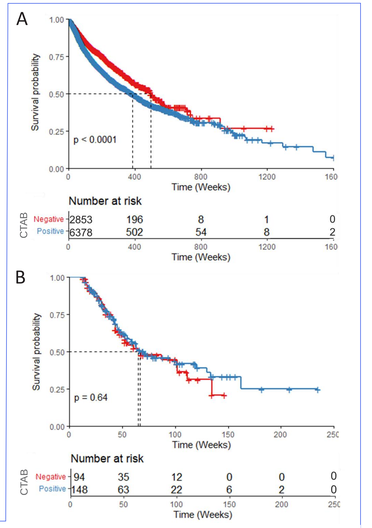

Figure 5: Kaplan-Meier survival analyses comparing CTAB positive (>=171) and negative (<171) groups for A) TCGA and B) retrospective cohorts.

Conclusions

- Our studies show that the CTAB distribution was maintained across the discovery and TCGA cohorts and a wide range of tumor types, supporting that the CTAB classifier is valid and histology agnostic.
- Additionally, when evaluating the ICB and non-ICB-treated cohorts, CTAB demonstrated the ability to predict OS, pointing to the utility of ICB in supporting CTA-specific natural immune response.
- However, further studies are necessary to verify these mechanisms of response to ICB as well as cancer vaccines and cell-based immunotherapies.
- Additional validation is needed to establish the predictive utility of CTAB alone and in combination with other immune oncology biomarkers for resistance or response.

References

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Presented at AACR 2022 | IM02 | Immunotherapy, Preclinical and Clinical

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