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Diverse RNA expression patterns of T cell priming markers in various solid tumors and their clinical implication

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BACKGROUND

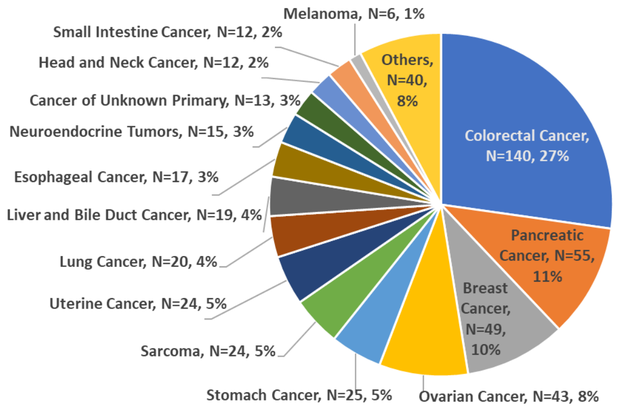
- Despite the success of immune checkpoint blockade in the management of advanced cancers, only a portion of patients will respond.
- One of the potential approaches to better immunotherapy involves performing clinical trials that are centered on stimulating cancer immunity through T cells.
- The genes associated with T cell priming are called T cell priming markers (TPM), including, but not limited to CD137, CD27, CD28, and CD80.
- However, the preliminary results from clinical trials to date are not very promising despite the strong scientific rationale; the response rate is approximately 0-20 % in most of the trials with immune-stimulating factors.[1,2]
- One possible explanation for the limited response rate is the heterogeneity of cancer immunity.
- This study aimed to interrogate the diversity of T cell priming marker RNA expression across cancers and to determine any correlations with canonical immunotherapy markers such as PD-L1 expression, TMB and/or MSI status.

METHODS

- We analyzed TPM expression in 514 samples of patients with wide variety of cancer.
- RNA expression was quantified by RNA sequence at OmniSeq laboratory.
- Transcript abundance was normalized to internal housekeeping gene profiles and ranked (0-100 percentile) to standardized by internal a reference population of 735 tumors spanning 35 histologies. The expression profiles were stratified by rank values into “Low” (0-24), “Intermediate” (25-74), and “High” (75-100).
- The similarity of each sample’s T cell priming markers expression were visualized on the two-dimensional field using principal component analysis.[3]
- R packages “tidyverse”, “cluster”, “factoextra” and “dendextend” were used for these analyses. P values were calculated by chi-square test for categorical values. For continuous values, two-sided t-test was used to calculate p values. Statistical significance was determined by $p < 0.05$ with Bonferroni correction for multiple comparisons.
- All investigations followed the guidelines of the UCSD Institutional Review Board for data collection (Study of Personalized Cancer Therapy to Determine Response and Toxicity, UCSD_PREDICT, NCT02478931) and for any investigational therapies for which the patients consented.

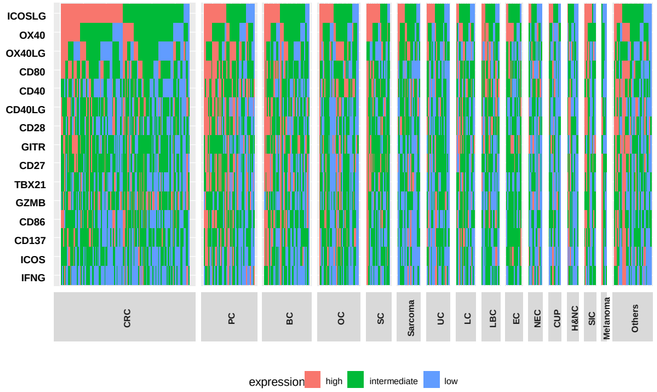
RESULTS

Cancer histologies included in the cohort (N = 514)



RESULTS

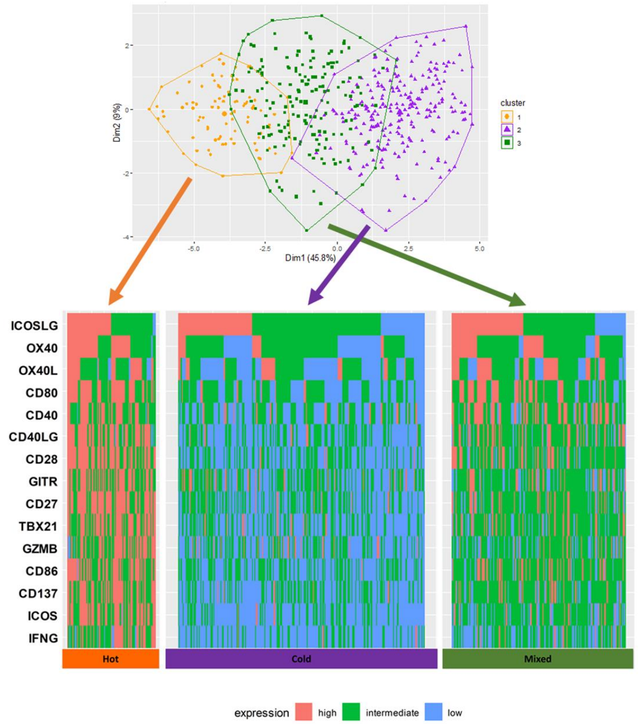
Diverse expression pattern of T cell priming markers in each histology of cancer



Transcript abundance was normalized to internal housekeeping gene profiles and ranked (0-100) to standardized by internal a reference population of 735 tumors spanning 35 histologies. The expression profiles were stratified by rank values into “Low” (0-24), “Intermediate” (25-74), and “High” (75-100).
97.7 % (n = 502) of patients had unique expression patterns of 15 T cell priming markers.
Abbreviations: BC: breast cancer, CRC: colorectal cancer, CUP: cancer of unknown primary, H&NC: head and neck cancer, LBC: liver and bile duct cancer, LC: lung cancer, NEC: neuroendocrine cancer, OC: ovarian cancer, PC: pancreatic cancer, SC: stomach cancer, SIC: small intestine cancer, UC: uterine cancer

RESULTS

Three clusters were defined based on TPM expression patterns, and they were significantly correlated with PD-L1 expression.

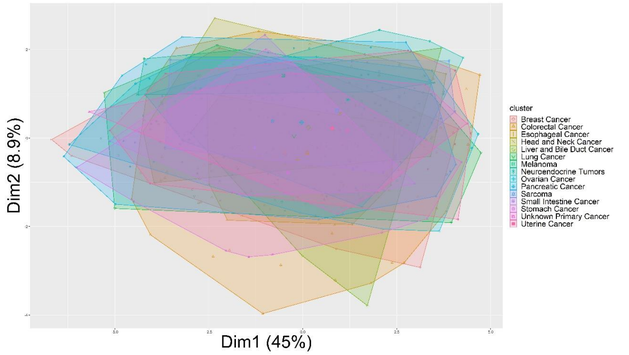


Other variables	Hot cluster (N=61) N (%)	Cold cluster (N=203) N (%)	Mixed cluster (N=124) N (%)	P value
MSI Unstable	4 (6.6 %)	3 (1.5 %)	7 (5.6 %)	0.059
TMB≥10 mutations/mb	6 (9.8 %)	15 (7.4 %)	10 (8.1 %)	0.83
PDL1 ≥ 1%	27 (44.3 %)	44 (21.7 %)	50 (40.3 %)	**< 0.001**
Colorectal Cancer	15 (24.6 %)	62 (30.5 %)	34 (27.4 %)	0.94
Pancreatic Cancer	8 (13.1 %)	14 (6.9 %)	15 (12.1 %)	0.17
Breast Cancer	9 (14.8 %)	20 (9.9 %)	11 (8.9 %)	0.44

Patients were clustered into three clusters by Ward’s hierarchical clustering method.[4] Orange, purple and dark green dots on the principal component analysis represent the patients classified into cluster 1 (Hot), 2 (Cold), and 3 (Mixed), respectively.

RESULTS

TPM expression patterns were not associated with histologies.



Silhouette score is a value calculated by intra-cluster and extra-cluster distance which demonstrates how well samples are clustered with other samples that are similar to each other. The values range from -1 to 1, with 1 meaning clusters are clearly separable, and -1 suggesting the clustering cannot be established. In this analysis, the silhouette score was -0.096, compared to a mean of -0.011 obtained in repeated randomized tissue assignments.

CONCLUSIONS

- The diversity of TPM expressions among various types of cancer was demonstrated.
- The expression pattern of TPM was significantly associated with PD-L1 status, but not with cancer histologies.
- Interrogating each patient’s immunome rather than specifying a histologic type of cancer may be necessary to increase success rate of clinical trials on immune stimulatory agents for cancer.

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