Identify associations between mutational signatures and immune cell infiltration

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Introduction:

Cancer is one of the most dangerous diseases throughout the world. According to the data presented by the World Health Organization, cancer is the second leading cause of death globally and was responsible for 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths is due to cancer. Although the death rate of cancers has decreased by 20% with the help of new diagnostic and surgical techniques, radiotherapy and chemotherapeutic drugs with novel targets in the past 20 years[1], obstacles such as drug resistance, relapse and malignant transfer have not yet been completely resolved[2].

Immune system is important to protect the body from multiple diseases, and its protective response against malignant cells have been studied with clinical evidence[3]. During immune response, several types of leukocytes will get activated, migrate and infiltrate the tumor. Those tumor-infiltrating immune leukocytes include Cytotoxic T lymphocytes, regulatory T lymphocytes, T helper lymphocytes, natural killer cells, dendritic cells, myeloid-derived suppressor cells (MDSC) and macrophages, all of which play important role in anti-tumor effects. As such, immunotherapy emerged as a novel cancer treatment option. Currently, response towards immune therapy is suboptimal; only 18-38% of treatment recipients mounted prolong responses[4,5]. To improve patient response, multiple efforts have been made to understand tumor-infiltrating lymphocytes(TILs)[6]. Utilizing TCGA database and bioinformatics tools, subpopulations of TILs were identified, and high adaptive immunity indicated good response to treatment[6].

Besides tumor infiltration status, tumor genetic alteration also is a key point of cancer therapy research. For cancers, certain mutation pattern of base substitution are recurrent, and these mutations signatures have been identified as markers across cancer types[7]. Mutational signatures, such as C>T and C>G, has been shown to highly correlate with breast cancer and melanoma[7]. Connections between mutational signature and immune infiltration had been investigated in breast cancer, where high APOBEC-type mutations(C>T,C>G) are associated with high expression of TIL-signature genes[6]. Additionally, mutation signatures are also known to be related to life styles as well. Tobacco usage have high G>T changes[8], Aristolochic acid exposure increase A>T and T>A alterations[9], and UV radiation increases CC>TT substittutions[10].

As mutational signatures of patients have predictive power in indicating immune infiltration of tumor as well as immunotherapy response, expanding such analyses beyond breast cancer could bring benefit in improving current immunotherapy. Significance found through

these correlation analyses would also give lights to patients' life style, and help physicians incorporate such aspect in their recommendation on treatment regimens. With such knowledge, we propose to conduct a pan-cancer analysis in correlating mutational signatures with tumor immune infiltrations. We, therefore, hypothesized that specific mutational signatures across cancer types can be used as markers to indicate patient immune response.

Methods:

DATA & FEATURES SELECGTION: In this study, we will be utilizing TCGA dataset for a holistic surveying on cancer types and patient records. Patient's DNA and RNA information from different kinds of solid tumors would be extracted through R's TCGAbiolinks package. Mutation calls of each patient would be used to filter for mutational signatures of interested. Specific mutational signatures are limited to G>T, T>A, A>T and CC>TT for the sake time limit of this project. RNA expression level of each patient will be input into CIBERSORT to identify immune cell profile and TILs. Correlation analyses would be performed to find specific mutation signatures that are associated with immune infiltration either across tumors or for specific tumors. Key immune cells that are sensitive to such mutation signature would also be identified and selected out. Benjamini-Hochberg's False Discovery Rate correction method would be applied to identify significantly correlated mutation signature and immune infiltrates.

PREDICTION OF THERAPY OUTCOME: In order to accurately understand mutational signatures, tumor immune infiltrations and their relationship with immunotherapy outcome, studies in TCGA that performed immunotherapy would be pulled using R. Using K-Fold validation methods, mutation signature and immune infiltrates would be used as features to train on immune therapy outcomes, and trained model will be tested on the left-out samples.

MUTATION SIGNATURE ENRICHMENT: Once key mutation signatures are found, expression analyses and functional enrichment for genes containing such mutation signature would be performed.

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