VISTA is a negative regulator of T-cell and myeloid cell function and is a target for cancer immunotherapy [1-3]. VISTA is highly expressed in tumor-infiltrating leucocytes, particularly within the myeloid lineage. Recent evidence suggests that tumor cells themselves also express VISTA, exacerbating the immunosuppressive milieu within the tumor microenvironment [4,5]. Determining tumor subtypes that overexpress VISTA can inform the indication selection for VISTA-targeting agents and design of clinical trials in specific patient populations.

Quantitative immunofluorescence (QIF) of VISTA protein expression was run on cancer tissue microarrays (TMA): breast (n=384), colon (n=597), lung (n=254), ovarian (n=275) and triple negative breast (n=196). Tumor compartment was defined by cytokeratin and DAPI staining. Localization of VISTA protein expression within the tumor compartment was seen in cores across different tumor types tested (Figure A). Percentage of cores demonstrating VISTA expression in tumor cells range from 4-15%, with highest frequency in colon cancer (Table B). Work conducted by Boger et. al. [4] and Zauderer et. al. [6] also show tumor expression of VISTA in gastric cancer and mesothelioma, respectively (Table C).

Genome-scale multi-omics data was obtained from the TCGA Pan-Cancer Atlas dataset. Previously published molecular signature was utilized to establish a leukocyte infiltration score for each individual tumor sample [7]. The immune cell component of VISTA expression was modeled using a nonlinear non-parametric regression model (LOESS). Samples which are 1.5 residues away from the regression curve demonstrating high VISTA expression independent of leukocyte infiltration were selected as likely demonstrating VISTA expression on tumor cells (Figure A). Utilizing this analysis, 703 of the 10,984 tumor samples (6.4%) in the TCGA were identified. VISTA expressing tumors were significantly enriched (hyper-geometric test, P<0.01) in several of the 33 cancer types (Figure B). Additionally, subpopulations of other cancers also exhibit VISTA expression in the tumor compartment (Table C).

Pathways associated with VISTA expressing tumors

TCGA Pan-Cancer Atlas dataset was further utilized to identify pathways associated VISTA expression on tumor cells. Three hundred eighty-seven genes were selected based on differential gene analysis conducted between sample which either had high or low VISTA expression independent of leukocyte infiltration. These genes were enriched in 26 pathways.

Summary

Detection of VISTA expressing tumors via two different methods presented here, show similar prevalence in overlapping tumor types in two independent datasets. These methods can be used to provide personalized therapy in the growing immuno-oncology era. For tumor types, such as mesothelioma, where prevalence of VISTA positive tumors are high selection may not be necessary to identify those sensitive to VISTA-targeting agents. In addition, a better understanding of associated pathways may drive better combination strategies.