Relative contribution of tumor infiltrating B cells to the tumor microenvironment assessed using an immuno-oncology focused multi-tumor tissue

M Bhagat[1], L Memeo[1], C Womack[1], WH Kim[2], M Cumberbatch[1]

[1]TriStar Technology Group, LLC, 1901 Pennsylvania Ave NW, Washington, DC 20006, USA, [2]Seoul National University Medical College, Seoul, South Korea.

TriStar Technology Group

Poster: 4646

Background

Although cancer immunotherapy approaches have focused primarily on driving T cell mediated immunity, attention has turned to other immune cell types within the tumor microenvironment (TME) to improve efficacy. Growing evidence supports a role for tumor-infiltrating B cells in complementing T cell-mediated immunity and contributing to the immunomodulation of cancer. Analyses of RNA sequencing data from The Cancer Genome Atlas (TCGA) have correlated high expression of B cell genes with improved patient survival in a range of cancer types. However, it is likely that effective anti-tumor immunity involves interactions between both B and T cells.

Methods

To investigate the relative contribution of B cells to the overall TME across multiple tumor types simultaneously, we have examined a multi-tumor tissue microarray (TMA) comprising 29 different cancer types represented by approximately 12 unique donors per indication and duplicate 1mm cores per donor (1 from invasive margin [IM] and 1 from tumor center [TC]). Serial sections were stained by single-plex immunohistochemistry for CD20 , CD3, CD4 and CD8, and immune cells enumerated by digital image analysis (CellProfiler™).

Results

- Analysis of overall B cell infiltration regardless of core location (IM and TC combined) revealed tumor indications such as lung, gastric, cutaneous SCC, ER+ breast and cervical cancers to exhibit the highest B cell densities (**Figure 1**). GIST, GBM, prostate, liver and pancreatic cancer displayed lowest B cell numbers.
- B cell densities correlated with T cell densities for most tumor types with some notable exceptions including, for example, ER+ BC and gallbladder cancer where the proportion of B cells was higher relative to T cells, and TNBC where the converse was evident (**Figure 2A**). Pie charts depicting T cell to B cell ratios illustrate those tumor types with higher numbers of infiltrating B cells relative to T cells in the TME (**Figure 2B**).
- The spatial distribution of B cell infiltration in the TME varied with some tumor donor cores showing clear evidence of organization of B cells in tertiary lymphoid structures (**Figure 3A**), whereas for other samples B cells were dispersed with T cells through the TME (**Figure 3B**). Different patterns of B cell distribution in the TME relative to other immune cells may impact the nature of cell interactions and therefore immune biology within those tumors.
- Spatial analyses revealed increased B cell densities in IM compared with TC, correlating with the distribution of T cells in the TME for the majority of tumor indications. However, a contrasting expression pattern was observed for tumor types such as cutaneous SCC and ER+ breast cancer where more highly infiltrated in TC than IM (**Figure 4**).

Conclusions

- Taken together, we describe the relative distribution of B cells in the TME across multiple tumor types simultaneously.
- This approach demonstrates the benefits of utilizing an immuno-oncology focussed multi-tumor TMA to interrogate B cell biology and to dissect how heterogeneity of this cell population may contribute to anti-tumor immunity.

Email contact: m.bhagat@tristargroup.us or m.cumberbatch@tristargroup.us

Figure 1

Comparison of B cell infiltration across tumor types

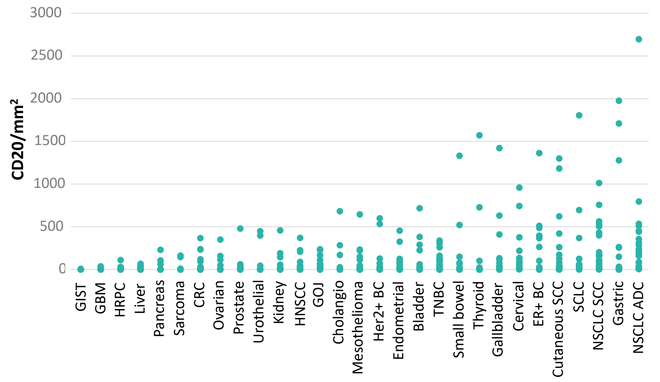

Figure 1. Comparative assessment of CD20+ infiltrating B cells for multiple tumor types. Data are plotted as CD20/mm² per core for all cores/tumor type regardless of location (IM or TC) in order of increasing mean B cell frequencies. N=24 cores/tumor type except GIST (10), sarcoma (18), CRC (48), thyroid (20), SCLC (18), NSCLC SCC (26).

Figure 2

Variable contribution of B cells to the TME across tumor types

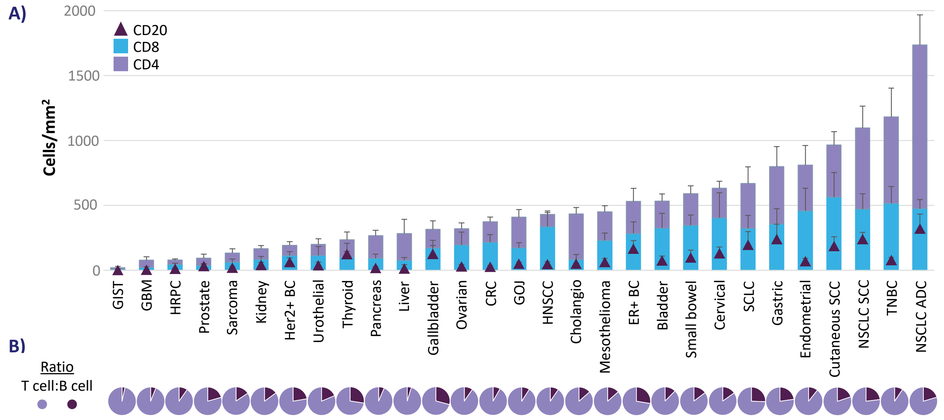

Figure 2. Tumor infiltration of T cells (CD4 ■; CD8 ■) plotted as mean values (±SE) for cells per mm² for all cores per tumor type regardless of location (IM and TC), in the context of mean (±SE) CD20 B cell (▲) frequencies. Data are plotted in increasing order with respect to total T cell content.

Figure 3

Representative images showing relative distribution of CD20+ B cells and CD3+ T cells

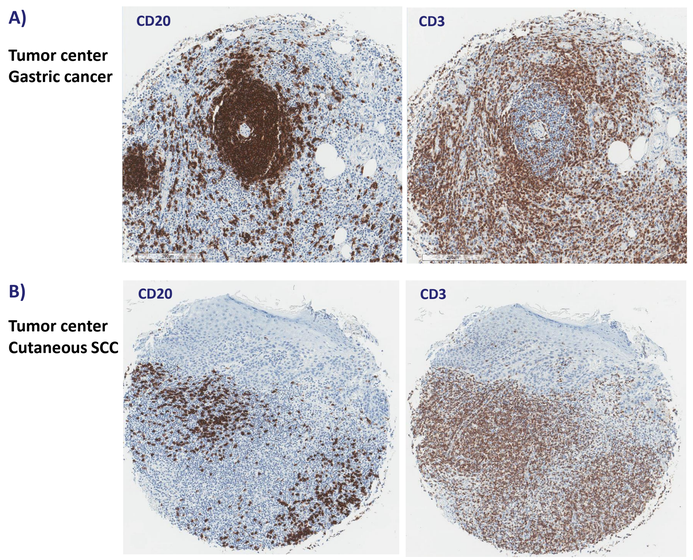

Figure 3. B cell infiltration was observed in organized tertiary lymphoid structures (**A**), or interspersed with other immune cells in the TME (**B**).

Figure 4

Spatial distribution of B cells in invasive margin vs tumor center

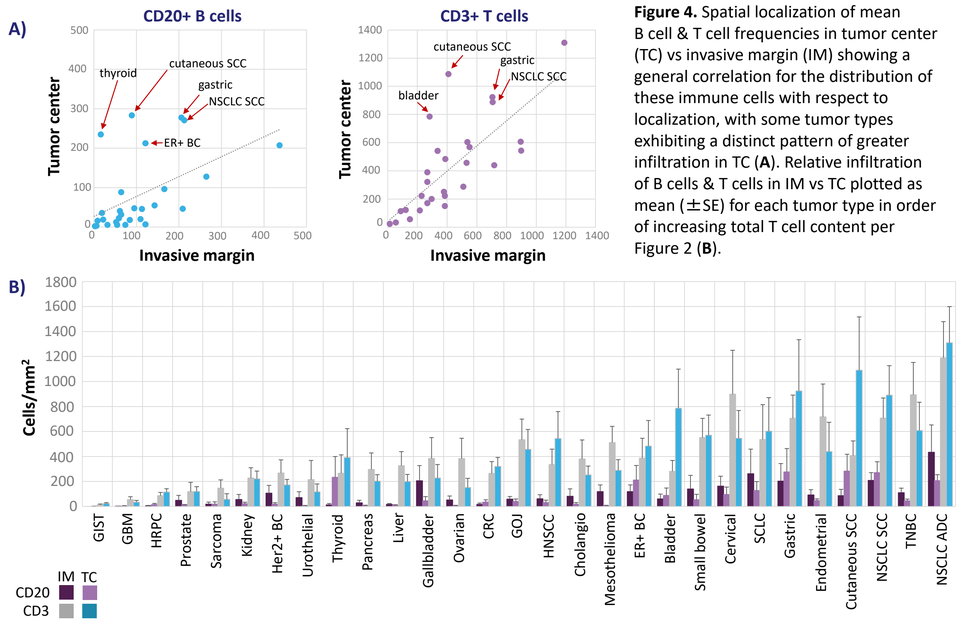

Figure 4. Spatial localization of mean B cell & T cell frequencies in tumor center (TC) vs invasive margin (IM) showing a general correlation for the distribution of these immune cells with respect to localization, with some tumor types exhibiting a distinct pattern of greater infiltration in TC (**A**). Relative infiltration of B cells & T cells in IM vs TC plotted as mean (±SE) for each tumor type in order of increasing total T cell content per Figure 2 (**B**).