Spatial profiles of tumor-infiltrating T cells

Xuefei Li[1], Ting-Fang He[2], Peter P. Lee[2], and Herbert Levine[1,3]

Short Abstract — **Higher amount of tumor infiltrating T cells has been demonstrated to associate with better prognosis in various types of cancer. However, the mechanism underlying different infiltration levels is still not clear. Here we focus on charactering the spatial infiltration pattern of T cells around tumor-cell clusters in patients with triple negative breast cancer. Combining mathematical modeling with patient data analysis, we propose that there exists an undefined factor that repels T cells away from tumor-cell clusters.**

Keywords — **tumor-infiltrating T cells, spatial profiles, tumor-cell clusters, repellent**

I. Background

ACTIVATED T lymphocytes have been demonstrated to be able to kill antigen-specific cancer cells via various mechanisms [1]. Not-surprisingly, stronger infiltration of cytotoxic T cells into tumor/tumor-cell-clusters generally associates with better prognosis, which has been demonstrated in various cancer [2-5].

There have been efforts on quantifying the distribution of cytotoxic T cells on the whole tumor level [6]. On the other hand, a solid tumor is usually composed by many tumor-cell clusters as well as stromal contents in gaps between those clusters. It has been noticed that T cells can be mostly constrained in the stromal regions of a solid tumor [7]. Therefore, it is also important to quantify the spatial pattern of T cells on the tumor-cell cluster level and further investigate the mechanism underlying the observed limited infiltration.

II. Results

In this work, based on images of immune cells and cancer cells (triple negative breast cancer, patient samples), we developed a procedure to estimate the spatial profile of immune-cell density and a few properties of those spatial profiles were observed

A. T-cell profiles correlate well with potential Antigen-Presenting cells

First, we simply calculated the fraction of each type of immune cells inside tumor-cell clusters. The fraction of T

cells is plotted against that of potential antigen-presenting cells (two types investigated here). It is observed that the fraction of T cells inside tumor-cell clusters can separate 18 patients into 2 groups, with 4 patients having the fraction above 0.4 and others below 0.2, whereas the fraction of each antigen-presenting cells is rather continuous for different patients. One interpretation of the plot is that the infiltration of T cells is bistable as a function of the infiltration of the potential antigen-presenting cells.

Secondly, we further investigated the detailed spatial profile of those cells inside/outside tumor-cell clusters. In 12 out of 15 patient samples analyzed, spatial profiles of T-cells correlate very well with at least one type of potential antigen-presenting cells.

B. T-cell density profile is better explained by a mathematical model hypothesizing a global attraction and local repulsion between T cells and cancer cells

Two types of mathematical models were developed: i) the motility of T cells decreases around tumor-cell clusters, or ii) the direction of motion of T cells is manipulated by tumor-cell clusters. One major difference between the two types of models is that the second model can generate a steady-state profile of T cells around tumor-cell clusters, which is favored since we did not observe any cancer-stage-dependent trend on the infiltration pattern.

III. Conclusion

Combining data analysis with mathematical modeling, we propose that innate immune cells actually promote the infiltration of T cells into tumor-cell islands and there exist a factor that repels T cells away from tumor-cell islands.

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[1]Center for Theoretical and Biological Physics, Rice University, Houston, TX, 77030 E-mail: xuefei.li@rice.edu

[2]Department of Immuno-Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA 91010 E-mail: the@coh.org and plee@coh.org

[3]Department of Bioengineering, Rice University, Houston, TX 77030 E-mail: herbert.levine@rice.edu