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Modeling the Recruitment of Tumor-Infiltrating T Lymphocytes

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The adaptive immune response to nascent cancerous lesions involves the activation of T cells, by antigen presenting cells (APCs) such as dendritic cells (DCs), followed by the recruitment of tumor infiltrating T lymphocytes (TILs) to the inflamed tumor site. Tissue resident T memory (TRM) cells have recently been identified as another arm of immune response [1, 2]. Indeed, higher levels of TRM cells in tumors correlates with favorable prognoses for different cancers [2]. Understanding the mechanisms underlying this correlation would be instrumental towards the development of more effective immunotherapeutic interventions, perhaps targeting TRM cells. In this respect, an agent-based model of tumor growth is proposed to shed light on how TRM cells might be controlling cancer growth and to study the potential mechanisms underlying the correlation between tumor presence of TRM cells and favorable disease prognoses. The proposed model, implemented using NetLogo [3], represents a 2-dimentional tissue section populated by normal cells, with a single cancer cell at its center, while a fixed fraction of cells making up the tissue are designated as TRM cells . The recruitment of TILs follows a stochastic model where the frequency of recruitment events is generated by a sigmoid function of the magnitude of inflammation in the tumor microenvironment (TME). The choice of this nonlinearity reflects the positive cooperation of molecular actions encountered in biological processes, and which applies to inflammatory cytokines in this case. The sigmoid slope is a free parameter reflecting the degree of TIL infiltration permitted by the TME.

The diversity of simulated tumor growth trajectories resulting from varying the proportion of TRM cells that are within the vicinity of cancer cells, provides a model illustration supporting the finding that distance between cancer and immune cells impacts clinical outcome. Indeed, successful killing of cancer cells by TRM cells results in local inflammation, which in turn drives the recruitment of TILs to the tumor regions where TRM cells were effective. Furthermore, the model suggests that the spatial distribution of TRM cells has a pivotal role in shaping tumor growth dynamics. However, further explorations are needed to take in consideration the metabolic stress caused by cancer cells as well as account for their immunosuppressive effects, which limit the cytotoxic effectiveness of immune cells [4]. In addition, further mathematical modeling would be needed to explore other related questions, such as: why tumors still develop in the presence of tissue resident T memory cells?

References

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