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Resident Breast T-cells: The Troops Are Already There

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Abstract

The role of tissue-resident memory T-cells (T_{RM}) in breast cancer progression has been difficult to study. Savas et al. used single cell RNA sequencing to identify T_{RM} cells in triple-negative breast cancer (TNBC) patients and demonstrated their prognostic value for predicting survival.

Single-cell transcriptome sequencing has emerged as a powerful unbiased technology for resolving cell types and states in human tissue, however its application to immune profiling is only beginning to be realized^{1,2,3}. Traditional methods such as flow cytometry and immunohistochemistry can only enumerate immune cell types using a limited number of established markers. In this study, Savas et al.⁴ applied single cell transcriptome sequencing to study triple-negative breast cancer (TNBC) tumor tissues and delineate the transcriptomic profiles of tumor-infiltrating T cells (TIL). This study clearly identified the presence of $CD8^+$ TIL harboring features of tissue-resident memory T cells (T_{RM}) in TNBC and demonstrated superior prognostic value of a new $CD8^+$ T_{RM} gene signature over $CD8$ expression for predicting survival of TNBC patients.

T_{RM} are a subset of memory T cells distinct from effector memory T cells (T_{EM}) in that they are non-recirculating and reside in the tissue to enhance the site-specific re-infection response. Resident memory T cells are classically defined by expression of molecules which help maintain their presence in tissue, mainly including $CD69$ and often the $\alpha E\beta 7$ integrin ($CD103$). Because of their rapid re-infection response, T_{RM} have predominantly been studied for anti-pathogen response in barrier tissues such as the gut mucosae and the skin⁵, but their role and frequency in breast tissues is not well established. A role for T_{RM} in the control of solid tumors has been proposed and the co-expression of $CD8$ and $CD103$ in the tumor has been associated with improved survival for several tumor types, including basal-like breast cancer⁶.

In their study, Savas et al. performed high-throughput single cell RNA sequencing on tumor-infiltrating T cells using a microdroplet platform (10X Genomics). Though they only examined two tumors by single cell sequencing, they were able to identify five CD4⁺ and four CD8⁺ T cell clusters, including an unexpected CD8⁺ T_{RM}-like population that they elected to investigate further. Previous studies in mouse dermis have shown CD8⁺ T_{RM} to have the potential to be very effective cytokine producers and to be superior to T_{EM} in their re-infection response⁷. Savas et al. show that this may also be true of T_{RM} in human breast cancer tissue with the single-cell T_{RM}-like population expressing more granzyme B transcripts than the T_{EM}-like population. Furthermore, a subset of the T_{RM} population appeared to be proliferating based on their expression of cell cycle genes, indicative that the population is expanding in response to tumor antigens. The authors further substantiated this finding by bulk RNA sequencing of FACS-sorted CD103⁺ and CD103⁻ populations of CD8⁺ T cells from three additional TNBC tumors, finding significantly higher granzyme B and perforin expression in the CD103⁺ population, implying a greater cytotoxic function.

The CD8⁺ T_{RM} TNBC TIL described in this study are clonally distinct and have featured of highly proliferative and cytotoxic T cells, all elements typically associated with a productive anti-tumor immune response. Savas et al. evaluated the prognostic potential of this CD8⁺ T_{RM} population computationally by leveraging the METABRIC expression data from primary TNBC tumors that were treated with chemotherapy, for their presented T_{RM} gene signature. They found that patients in the top quartile of expression for the T_{RM} signature had significantly longer overall survival and disease-free survival than those in the lower quartiles indicating the potential clinically prognostic role of this memory T cell subset. However, in contrast to previous studies⁸, they did not find CD8 expression alone to be prognostic in TNBC.

In summary, Savas et al. demonstrate the presence and prognostic importance of tissue-resident memory CD8⁺ T cells in TNBC tumors. This provides a significant stepping stone for future work. Emerging data supports a role for T_{RM} in tumor immunity, but more work needs to be done to clarify their exact contribution to tumor clearance and to design interventions to sustain their activation. Understanding the potential involvement of T_{RM} in the tissue-specific break down in immune surveillance allowing cancer cells to develop in the first place may also be very important going forward. This would require the characterization of T_{RM} in non-diseased breast tissue in large cohorts of patients with long-term clinical followup data to understand the potential associated risk of developing invasive breast cancer. However, this may prove difficult because in the absence of disease to provoke a response, T_{RM} could prove to be very rare cells in normal breast tissue (as the authors demonstrated in a few cases of prophylactic mastectomies from normal women). Nevertheless, in the age of immunotherapy even rare anti-tumor immune populations may prove to be clinically important in deciding which patients to treat. Specifically targeting genes and pathways in Trm cells in TNBC patients may improve responses in immunotherapy, which, despite intensive investigation, have been underwhelming in clinical trials.

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Figure 1 - Effector Functions of Tissue-resident Memory T-cells in the Breast

In triple-negative breast cancers, the tissue resident memory T-cells have higher effector functions for killing tumor cells compared to circulating T-cells that enter the tissues.