Single-Cell Treg profiling: new cancer therapies and insights into tumor-Treg biology

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Abstract

Conventional CD4+ T cells (Tconvs) play a diverse role in cancer immunology by directly destroying tumor cells, and indirectly by supporting the effector function and differentiation of CD8+ T cells and B cells. Conversely, regulatory CD4+ T cells (Tregs) contribute to the development of cancer by imposing an immunosuppressive microenvironment. Thus, CD4+ T cells constitute a group of different subsets that orchestrate the balance between pro-inflammatory and immunosuppressive responses, both locally in the tumor and in tumor-draining lymph nodes (LNs), where the adaptive immune response is initiated. Despite their central role, the contribution of LNs to anti-tumor immunity has remained underexplored. We conducted an integrative single-cell analysis of transcriptome, T-cell receptor (TCR) repertoire, and chromatin accessibility profile of CD4+ Tconvs and Tregs, from the blood, LNs, and tumors of treatment-naïve Non-Small Cell Lung Cancer (NSCLC) patients.

On the fundamental side, we identified a subgroup of CD4+ T cells with a shared regulatory program involving TCR activation, tissue residency, and follicular characteristics. These cells, governed by a BATF-driven program, were named Follicular and Tissue-Adapted (FTA) cells. FTA cells are found in active germinal centers in the LNs and in tertiary lymphoid structures in the tumor, and exhibit significant enrichment for shared tumor specificities, suggesting their implication in shaping the anti-tumor immune response. Additionally, our findings offer fundamental new insights into the biology of follicular Tregs, which will be presented.

On the translational side, we discovered a tumor-associated Treg subset that is clonally expanded, shows signs of TCR-mediated activation, and expresses a unique gene signature, making them amenable to specific therapeutic targeting. This discovery led to the development of novel immunotherapeutic strategies, currently under evaluation in an early-stage clinical trial, aimed at enhancing anti-tumor immunity while minimizing systemic immune suppression.

Biography

Dr. E. Piaggio earned her clinical biologist diploma and a Ph.D. in Immunology from the National University of Rosario in Argentina. She pursued post-doctoral research in France and is now a research director at INSERM. Dr. Piaggio leads the "Translational Immunotherapy" team at Institut Curie in Paris, which is part of France's first Center for Cancer Immunotherapy. Her research has significantly advanced regulatory T-cell-based immunotherapy across several domains, including infectious diseases (Chagas' disease), autoimmune disorders (type 1 diabetes and multiple sclerosis/EAE), alloreactivity (GVHD and transplantation), and more recently, cancer. In addition to her academic work, she is a co-founder of Egle-Therapeutics, a biotechnology company specializing in Treg-based immunotherapies.