PROJECT

Supervisor:	Dr. Francesco Andreata
Title:	Computational dissection of dendritic cell–CD8 T-cell circuits in hot and cold tumor microenvironments
Curriculum:	Basic and Applied Immunology and Oncology

Link to the personal page of the University or relevant hospital site website:	https://www.unisr.it/docenti/a/andreata-francesco

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

CD8⁺ T cells are the main mediators of antitumor immunity and a major determinant of response to immunotherapy. However, their functional state varies substantially across tumor types and tissues. While some tumors are characterized by inflamed microenvironments that support effective cytotoxic T-cell responses, others develop highly immunosuppressive conditions in which CD8⁺ T cells become scarce, dysfunctional, or excluded from the tumor site. Increasing evidence suggests that these differences are strongly influenced by the tissue environment in which tumors arise. The liver, for example, is a highly tolerogenic organ in which immune responses are tightly controlled to prevent excessive inflammation, often resulting in impaired antitumor T-cell activity. In contrast, other tissues such as the lung more frequently sustain inflamed immune responses with T cell infiltrated tumors. Although dendritic cells play a central role in shaping CD8⁺ T-cell priming and differentiation, how tissue-specific dendritic cell programs contribute to the establishment of functional versus dysfunctional CD8⁺ T-cell states in liver cancer remains poorly understood.

Rationale and hypothesis

We hypothesize that tissue-specific microenvironments impose distinct transcriptional programs on CD8⁺ T cells through coordinated interactions with antigen-presenting cells and stromal components of the tumor microenvironment. Antigen presenting cells – particularly dendritic cells – play a key role in orchestrating adaptive immune responses, yet their functional programs may themselves be shaped by local tissue signals. Integrating single-cell and spatial transcriptomic datasets from different tumors and tissues provides a powerful strategy to reconstruct these regulatory circuits and identify tissue-imprinted immune programs.

Objectives and specific aims

This project will computationally investigate how dendritic cell programs shape $CD8^+$ T-cell dysfunction in liver cancer by integrating single-cell and spatial transcriptomic datasets from mouse models of hepatocellular carcinoma and human HCC samples. The study is specifically focused on defining biologically relevant and experimentally testable immune circuits within the hepatic tumor microenvironment.

Specific aims include: (i) reconstructing transcriptional states of $CD8^+$ T cells in liver cancer, with particular focus on functional, dysfunctional, and immune-excluded T-cell populations; (ii) identifying dendritic cell programs associated with these distinct $CD8^+$ T-cell states, including antigen presentation, costimulatory and inhibitory pathways, and tissue-imprinted tolerogenic signals; and (iii) reconstructing spatial and ligand–receptor interaction networks linking dendritic cells, stromal components, and dysfunctional $CD8^+$ T cells within the tumor microenvironment.

The final objective is to define candidate regulatory circuits that can be prioritized for experimental validation and may represent novel therapeutic targets to improve antitumor immunity in liver cancer.

Expected outcomes

The project is expected to define conserved and tissue-specific immune programs shaping $CD8^+$ T-cell function across cancers. By integrating immune, stromal, and spatial information across datasets, this work will provide a systems-level understanding of how tumor microenvironments regulate antitumor immunity. These insights may reveal candidate mechanisms underlying immune responsiveness or dysfunction and inform future strategies aimed at improving cancer immunotherapy.

Skills that the student should acquire (max. 600 characters including spaces):

The candidate will develop advanced skills in computational immunology and bioinformatics, including analysis and integration of single-cell and spatial transcriptomic datasets. The student will gain expertise in identifying immune cell states, reconstructing cell–cell interaction networks, and performing comparisons across mouse and human data. The project will also foster critical skills in data interpretation, hypothesis generation, and interdisciplinary research in tumor immunology. The candidate will participate in experimental design discussions and presentation of results in meetings.

References (max. 15)

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4. Kawashima, K., Andreata, F., Beccaria, C.G., and Iannacone, M. (2024). Priming and Maintenance of Adaptive Immunity in the Liver. 42. 10.1146/annurev-immunol-090122-041354. Annu. Rev. Immunol.

5. Bénéchet, A.P., Simone, G.D., Lucia, P.D., Cilenti, F., Barbiera, G., Bert, N.L., Fumagalli, V., Lusito, E., Moalli, F., Bianchessi, V., Andreata, F., et al. (2019). Dynamics and genomic landscape of CD8+ T cells undergoing hepatic priming. 574, 200–205. 10.1038/s41586-019-1620-6. Nature

6. Guidotti, L.G., Inverso, D., Sironi, L., Di Lucia, P., Fioravanti, J., Ganzer, L., Fiocchi, A., Vacca, M., Aiolfi, R., Sammicheli, S., et al. (2015). Immunosurveillance of the Liver by Intravascular Effector CD8+ T Cells. 161, 486–500. 10.1016/j.cell.2015.03.005. Cell

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8. Fumagalli, V., Venzin, V., Di Lucia, P., Moalli, F., Ficht, X., Ambrosi, G., Giustini, L., Andreata, F., et al. (2022). Group 1 ILCs regulate T cell-mediated liver immunopathology by controlling local IL-2 availability. 10.1126/sciimmunol.abi6112. Sci Immunol.