PROGETTO

Supervisore: **BALESTRIERI CHIARA**

Titolo/*Title:* Unraveling Mechanisms and Targeting Liver Metastasis in Pancreatic Cancer: Insights into the Metastatic Microenvironment

Curriculum: Terapia Genica e Cellulare/Gene and Cell Therapy

Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento: https://research.hsr.it/en/centers/omics-sciences/immunogenomics-lab/chiara-balestrieri.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

Pancreatic Ductal Adenocarcinoma (PDAC) is a highly heterogeneous disease, with liver metastases posing a significant threat to patient survival. Despite extensive genomic and transcriptomic studies on primary tumors, the driving mechanisms behind liver progression are not fully understood. The complex nature of these tumors demands advanced bioinformatic tools and workflows for comprehensive data analysis for example to elucidate immune niches that sustain PDAC in the liver microenvironment.

Rationale and hypothesis

With the rapid evolution of omics techniques, there's a pressing need for specialized software to handle the resulting complex datasets. Our project aims to bridge this gap by focusing on the development and application of advanced bioinformatic workflows tailored for the analysis of high-throughput data with the aim of dissect the complex interactions between tumor cells and the liver microenvironment. We will utilize innovative omics approaches, including spatial techniques like 10x Genomics Visium HD [1-2] and the GeoMx Digital Spatial Profiler [3], integrating them into a customized computational pipeline. This approach will enable us to gain a deeper understanding of tissue organization by merging insights from diverse omic platforms. Additionally, this project will contribute to the evolution of cancer genomics and bioinformatics by pioneering new methodologies for robust data interpretation.

Objectives and specific aims

Our project aims to dissect the complex interactions between tumor cells and the liver microenvironment using bioinformatics-driven analyses. Specific objectives include:

-Characterization of the liver metastatic microenvironment: Analysis of patient-derived samples will elucidate the cellular and molecular composition of microenvironment, including stromal components and immune cells, with the major aim of the identification of cellular niches characteristic of the disease.

-Studying the crosstalk between tumor and stromal cells: Utilizing patient-derived samples, we will define the cellular and molecular landscape, focusing on stromal components and immune cells in order to better elucidate their interaction in individual subjects.

-Role of immune cells: Integrating molecular profiling data, we will delve into immune cell profiles and immunosuppressive mechanisms to identify molecular targets crucial for liver metastasis. This will encompass signaling pathways and immune checkpoint molecules, guiding potential clinical trials.

Expected outcomes

This project aims to enhance our understanding of liver metastases in pancreatic cancer by profiling the localized cellular interactions that might sustain carcinogenesis,leveraging spatial transcriptomics techniques, and integrating them with other multi-omics approaches. Through the development and implementation of a specialized bioinformatic workflow, we anticipate revealing novel insights in the cell-cell interaction landscape of the PDAC with the final aim of identifying potential therapeutic targets. This data-driven approach will not only deepen our understanding of metastatic processes but also lay the groundwork for innovative therapeutic interventions to enhance patient outcomes.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

Following the PhD training, the student will develop a strong background in cancer molecular biology and immunology, enabling them to interpret complexity and understand underlying disease rules. They will gain expertise in NGS-based spatial analysis and enhance coding skills in Python and R. Additionally, they will develop competencies in cancer genomics and bioinformatics, contributing to the development of tailored methods for extracting knowledge from spatial maps and in the analysis and integration of spatial transcriptomics with other omics techniques, contributing to workflow design.

Bibliografia (max. 15)

[1] Burgess DJ, Spatial transcriptomics coming of age, Nat Rev Genet (2019)

[2] Moses L. & Pachter L., Museum of spatial transcriptomics, Nat Methods (2022)

[3] Hernandez S. et al. Challenges and Opportunities for Immunoprofiling Using a Spatial High-Plex Technology: The NanoString GeoMx® Digital Spatial Profiler, Frontiers in Oncology (2022)