PROJECT

Supervisor:	Nicoletta Caronni
Title:	Defining the role of inflammatory macrophages as drivers of pancreatic tumor initiation
Curriculum:	Basic and Applied Immunology and Oncology

Link to the personal page of the University or relevant hospital site website: https://research.hsr.it/en/institutes/san-raffaele-telethon-institute-for-gene-therapy/genomics-of-the-innate-immune-system/nicoletta-caronni.html

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

Background/gap of knowledge

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy with limited therapeutic options, and the mechanisms driving its initiation remain poorly understood. Increasing evidence indicates that inflammation plays a key role in pancreatic tumorigenesis. In particular, inflammatory signals generated during tissue damage can induce persistent transcriptional programs in epithelial cells, increasing their susceptibility to malignant transformation in the presence of oncogenic mutations. Within this inflammatory context, macrophages represent a major cellular component of the pancreatic microenvironment, and their abundance has been strongly associated with PDAC development and progression. We recently identified a pro-inflammatory subset of tumor-associated macrophages producing IL-1β that sustains cancer-promoting inflammation in PDAC. Notably, IL-1β^{+} macrophages are already present in early preneoplastic lesions and can also be detected in healthy pancreas following tissue damage, such as pancreatitis. However, the functional role of these macrophages during pancreatic injury and early tumorigenesis remains unknown.

Rationale and hypothesis

The presence of IL-1β^{+} macrophages both during pancreatic tissue damage and in early PDAC lesions suggests that this macrophage population may represent a mechanistic link between pancreatic injury and tumor initiation. Because macrophages are key regulators of inflammatory responses and epithelial plasticity during tissue repair, their activation may shape the inflammatory microenvironment that favors neoplastic transformation. We therefore hypothesize that IL-1β^{+} macrophages upon tissue damage sustain inflammatory signals that promote epithelial transformation and contribute to PDAC initiation.

Objectives and specific aims

The objective of the project is to define the role of IL-1β⁺ macrophages during pancreatic tissue damage and PDAC development.

Aim 1: Determine the dynamics of recruitment, spatial localization and cellular interactions of IL-1β⁺ macrophages in the pancreas following tissue damage.

Aim 2: Define how IL-1β⁺ macrophages functionally contribute to PDAC development during early tumorigenesis.

Expected outcomes

This project will define the temporal dynamics and functional role of IL-1β⁺ macrophages during pancreatic injury and tumor initiation. We expect to define how IL-1β⁺ macrophages shape the inflammatory microenvironment that supports PDAC development. These findings will provide mechanistic insight into the link between tissue damage, inflammation and pancreatic tumorigenesis and may identify new targets for early therapeutic intervention.

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

The candidate will develop critical thinking and scientific independence while gaining expertise in experimental and analytical approaches to study inflammation and tumor initiation. She/he will acquire experience with in vivo models of pancreatic injury and PDAC, flow cytometry and imaging techniques to study immune cell dynamics, and transcriptomic approaches including bulk, single-cell and spatial analyses. Through interaction with computational biologists, the candidate will gain familiarity with data analysis tools and interdisciplinary research.

References (max. 15)

1) IL-1β⁺ macrophages and the control of pathogenic inflammation in cancer. Caronni N, La Terza F, Frosio L, Ostuni R. **Trends Immunol, 2025.** PMID: 40169292.

2) Targeting PGE_2-IL-1β axis to impact future treatments for pancreatic ductal adenocarcinoma and its precursors. Camisa P.R., Caronni N, Crippa S. **Expert Review of Anticancer Therapy, 2025.** PMID: 39754391.

3) IL-1β⁺ macrophages fuel pathogenic inflammation in pancreatic cancer. Caronni N*, La Terza F, Vittoria FM, Barbiera G, […], Ostuni R*. **Nature, 2023.** PMID: 37914939.

4) Cellular and transcriptional dynamics of human neutrophils at steady state and upon stress. Montaldo E*, Lusito E*, Bianchessi V*, **Caronni N***, […]and Ostuni R. **Nature Immunology, 2022.** PMID: 36138183

5) A PGE_2-MEF2A axis enables context-dependent control of inflammatory gene expression. Cilenti F, Barbiera G, Caronni N, […], Ostuni R. **Immunity, 2021.** PMID: 34129840

6) TIM4 expression by dendritic cells mediates uptake of tumor-associated antigens and anti-tumor responses. Caronni N*, Piperno GM, […], Benvenuti F*. **Nature Communication, 2021.** PMID: 33854047

7) Determinants, mechanisms, and functional outcomes of myeloid cell diversity in cancer. Caronni N, Montaldo E, Mezzanzanica L, Cilenti F, Genua M, Ostuni R. **Immunological Reviews, 2021.** PMID: 33565148

8) Downregulation of trafficking proteins and conditioning by lactic acid determine loss of dendritic cells function in the tumor microenvironment. Caronni N, Simoncello F, Stafetta F, Guarnaccia C, Opitz B, Galli T, Proux-Gillardeaux V, Benvenuti F. **Cancer Research, 2018.** PMID: 29363545

9) ACKR2 in hematopoietic precursors as a checkpoint of neutrophil release and antimetastatic activity.

Massara M*, Bonavita O*, Savino B*, **Caronni N***, Sironi M, Mollica Poeta V, Setten E, Recordati C, Crisafulli L, Ficara F, Mantovani M, Locati M, Bonecchi R. **Nat Commun. 2018**. PMID: 29445158

10) Cancer and Chemokines. **Caronni N**, Savino B, Recordati C, Villa A, Locati M, Bonecchi R. **Methods Mol Biol, 2016.** PMID: 27033218

11) Myeloid cells in cancer-related inflammation. **Caronni N**, Savino B, Bonecchi R. **Immunobiol, 2015.** PMID: 25454487

12) ERK-dependent downregulation of the atypical chemokine receptor D6 drives macrophage infiltration and tumor aggressiveness in Kaposi's sarcoma. Savino B*, **Caronni N***, Anselmo A, Pasqualini F, Borroni EM, Basso G, Celesti G, Laghi L, Tourlaki A, Boneschi V, Brambilla L, Nebuloni M, Vago G, Mantovani A, Locati M, Bonecchi R. **Cancer Immunol Res, 2014.** PMID: 24844911