PROJECT 1

DoS: Prof. Lorenzo DAGNA

Title: Disentangling the cross talk between B cells and fibroblast in IgG4-related autoimmune pancreatitis and pancreatic adenocarcinoma

Curriculum: Experimental and Clinical Medicine

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https://www.unisr.it/docenti/d/dagna-lorenzo
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Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):

IgG4-related disease (IgG4-RD) is a fibroinflammatory disorder with a relapsing-remitting pattern (1). IgG4-RD has been clustered into four different phenotypes, namely the Pancreato-Hepato-Biliary group; the Retroperitoneal Fibrosis and/or Aortitis group; the Head and Neck-Limited group and the Mikulicz syndrome with systemic involvement group. Type 1 autoimmune pancreatitis (AIP) falls under the IgG4-RD spectrum being its most prevalent manifestation. Thus, AIP shows all IgG4-RD hallmarks, including the presence of a dense lymphoplasmacytic infiltrate rich in IgG4+ plasma cells in the affected tissue, abundant storiform fibrosis, and a clinical response to glucocorticoids and B cell depletion therapy (1).

Given the systemic nature of IgG4-RD, PET-FDG^{18} scan emerged as a potent diagnostic tool, simultaneously capturing multiorgan involvement and mirroring disease activity (2). Yet, PET scan is affected by an insufficient spatial resolution, a major caveat in focal AIP. In addition, pancreato-biliary malignancies might show FDG18 uptake as well. In this context the recently developed PET-MRI represents an asset in IgG4-RD, providing highly accurate metabolic and anatomic details in IgG4-RD patients.

Opposite to AIP, pancreatic ductal adenocarcinoma (PDAC) carries a dismal prognosis, being one of the most lethal malignant diseases (3). In apparent contrast with this aggressiveness, most of the tumor mass in PDAC is not made of malignant cells, but of a desmoplastic reaction consisting of cancer-associated fibroblasts (CAF) and immune cells. Of note, AIP and PDAC share some peculiar features, such as the dominant fibrotic core and a lymphoplasmacytic infiltrate rich in T lymphocytes and plasma cells. Moreover, focal AIP acts as a PDAC mimicker, often leading to overtreatment and unnecessary surgery.

As suggested by the clinical response to anti-CD20 therapy, B lymphocytes play a pivotal role in IgG4-RD pathogenesis (1). Yet, the contribution of B cells to IgG4-related fibrosis is still unresolved. Of note, recent reports showed that B cells promote PDAC progression but their interaction with the local stroma has been largely overlooked (3).

Aim of this project is to evaluate and compare the B cell – fibroblast crosstalk in AIP and PDAC. In particular, we will prospectively:

- study the baseline clinical and imaging characteristics (MRI-PET) of AIP patients;

- perform an extensive immune profiling with detailed immunophenotyping of circulating B cells at different time-points in AIP and PDAC patients;

- perform the same immune profiling studies on histological samples from core biopsy of patients with AIP and PDAC;

- evaluate serum marker of fibrosis at baseline and after therapy in AIP and PDAC;

- evaluate by *in vitro* experiment the interactions of each B cell subset with fibroblast obtained by core biopsy from PDAC and AIP patients at baseline;

- compare the findings from AIP patients with those obtained from the other three IgG4-RD phenotypes.

Skills to be acquired by the student:

Perform independent literature search, study planning, pose a research question/problem, examine the range of available modes of inquiry, identify the appropriate research mode and procedure, identify a data collection strategy. Acquire advanced knowledge of clinical immunotyping, its analysis and clinical/research relevance. Understand the fundamentals of genetic studies, their analysis and clinical/research relevance. Develop independent ability to analyze, interpret data, and draw conclusion from data, and to write a research paper.

References (max. 3)

1) Perugino, C.A., Stone, J.H. IgG4-related disease: an update on pathophysiology and implications for clinical care. Nat Rev Rheumatol 16, 702–714 (2020).

2) Berti A, Della torre E, Gallivanone F, et al. Quantitative measurement of 18F-FDG PET/CT uptake reflects the expansion of circulating plasmablasts in IgG4-related disease. Rheumatology (Oxford). 2017;56:2084-2092.

3) Feig C, Gopinathan A, Neesse A, et al. The pancreas cancer microenvironment. Clin Cancer Res. 2012;18: