PROJECT 1

DoS: Federica Ungaro

Title: **The role of MFSD2A in the resolution of colorectal cancer-promoting inflammation: implications for innovative therapies**

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page:

Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):

Inflammation is a recognized hallmark of cancer that contributes to the development and progression of several malignancies, including colorectal cancer (CRC) (1-3). Anti-inflammatory drugs currently used for the treatment of patients with CRC show many sides adverse effects (4-6) that prompted researchers to propose the specialized pro-resolving mediators (SPMs), derived from omega-3 polyunsaturated fatty acids (PUFAs), as promoters of resolution of cancer-associated inflammation (7). In 2017 we demonstrated that in patients with ulcerative colitis undergoing remission, the Major Facilitator Superfamily Domain-containing 2A (MFSD2A) oversees SPMs production by the gut vasculature, leading to the resolution of intestinal inflammation by upregulating the production of pro-resolving docosahexaenoic acid (DHA)-derived metabolites (8). We hypothesized that MFSD2A might drive the production of these SPMs also in patients with CRC. Our proposal aims to identify the MFSD2A-dependent pathways responsible for the resolution of tumor-associated intestinal inflammation, paving the way for a new avenue for the treatment of CRC.
To carry out this project, we propose to finalize the following aims:
WP1. To define the functional role of MFSD2A in orchestrating pro-resolving pathways in the intestinal endothelium of CRC patients.
-Task 1a. Enrolment of patients with metastatic CRC and Human Intestinal Microvascular Endothelial Cells (HIMEC) isolation.
-Task 1b. Identification of MFSD2A-dependent pro-resolving pathways in metastatic CRC.
-Task 1c. Functional validation of in silico results.
WP2. To generate an MFSD2A-inducible mouse model to assess the functional role of this protein in different phases of experimental CRC development.
- Task 2a. Investigation of the role of Mfsd2a in CRC development and metastasization process.
- Task 2b. Molecular characterization of tumors.
WP3. Evaluate the clinical efficacy of cell-specific Mfsd2a overexpression in experimental models of non-metastatic CRC.
- Task 3a. In vivo delivery of Mfsd2a during colorectal carcinogenesis.
- Task 3b. In vivo enhancement of pro-resolving process exploiting the CRISPRa system.

Skills to be acquired by the student (*Number of characters*, *including spaces*: max 600):

- Isolation of primary cells from surgical specimens
- Lentivirus production and lentiviral manipulation of primary cells
- Competences in lipidomics and transcriptomics analysis
- Animal handling and capability of performing experimental model of carcinogenesis
- In vivo administration of pro-resolving molecules for ameliorating CRC in animals
- Competencies in molecular and cellular biology techniques
- Capability to critically discuss results
- Capability to write reports and the final manuscript, along with the final thesis
- Independence in coordinating experiments, under DoS's supervision

References (max. 15)

1. Mantovani A, Garlanda C, Allavena P. Molecular pathways and targets in cancer-related inflammation. Ann Med. 2010 Apr;42(3):161–70.
2. Feagins LA, Souza RF, Spechler SJ. Carcinogenesis in IBD: potential targets for the prevention of colorectal cancer. Nat Rev Gastroenterol Hepatol. 2009 May;6(5):297–305.
3. Lakatos P-L, Lakatos L. Risk for colorectal cancer in ulcerative colitis: changes, causes and management strategies. World J Gastroenterol. 2008 Jul 7;14(25):3937–47.
4. Zhang Q, Zhu B, Li Y. Resolution of Cancer-Promoting Inflammation: A New Approach for Anticancer Therapy. Front Immunol. 2017 Feb 2;8:71.
5. Zhang Y, Liu L, Fan P, Bauer N, Gladkich J, Ryschich E, et al. Aspirin counteracts cancer stem cell features, desmoplasia and gemcitabine resistance in pancreatic cancer. Oncotarget. 2015 Apr 30;6(12):9999–10015.
6. Nelson N. On trial: evidence from using aspirin to prevent cancer. J Natl Cancer Inst. 2015 Sep 4;107(9).
7. Serhan CN, Chiang N, Dalli J. The resolution code of acute inflammation: Novel pro-resolving lipid mediators in resolution. Semin Immunol. 2015 May;27(3):200–15.
8. Ungaro F, Tacconi C, Massimino L, Corsetto PA, Correale C, Fonteyne P, et al. MFSD2A Promotes Endothelial Generation of Inflammation-Resolving Lipid Mediators and Reduces Colitis in Mice. Gastroenterology. 2017 Nov;153(5):1363-1377.e6.