PROJECT 1

DoS: Mirela Kuka

Title: In depth characterization of monocyte-B cell interactions in infection and cancer

Curriculum: BAIO

Link to OSR/UniSR personal page: https://www.unisr.it/en/docenti/k/kuka-mirela

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

Monocytes can contribute to the shaping of the immune response in different ways, either promoting immunity to pathogens, or being detrimental and causing an exacerbated inflammation. We have recently found that myeloid cells of monocytic origin interact with B lymphocytes and suppress antibody responses in the context of viral infections (1,2). Direct suppression of B lymphocytes by myeloid cells is an emerging concept that still needs to be fully investigated with regard to the molecular mechanism. Moreover, the context-dependent roles of myeloid cells should be investigated in different pathological settings. Indeed, inflammatory monocytes are recruited in response to different pathogens, however they do not suppress B cell responses in all settings. One possibility is that these differences might be imputed to a different timing of recruitment or persistence of these monocytes in the dLNs. Another possible explanation could be that inflammatory monocytes might change their phenotype once recruited in the infected organs.
Suppressive myeloid cells are also found in settings of cancer and autoimmunity. In the context of tumors, cells of monocytic origin with suppressive abilities have been named M-MDSC (monocytic Myeloid-derived Suppressor Cells), and along with their granulocytic counterparts (PMN-MDSC) have been reported to play a key role in suppressing anti-tumoral T cell responses. Conversely, how suppressive myeloid cells modulate the function of B lymphocytes infiltrating tumors has not been investigated yet. In particular, although the role of B cells in antitumor immunity is still debated, in some cancer settings the presence of B cell-containing tertiary lymphoid structures (TLS) correlates positively with cellular immune responses against the tumor (3). Therefore, unleashing of the antitumor potential of B cells might lead to the identification of new antigens and of new immunotherapeutic approaches.
The goal of this project is to characterize at the cellular and molecular levels how monocyte-B cell interactions influence the humoral response in the context of viral infections and tumor. To address this goal, the student will pursue the following aims:

1. Characterization of the phenotype of myeloid cells interacting with virus-specific B cells as well as the molecular mechanism leading to B cell suppression. The student will characterize and compare monocyte recruitment kinetics upon viral infections and immunization approaches, and their impact on B cell fitness. In addition, experiments aiming at evaluating the monocytes phenotype plasticity in which monocytes from different conditions will be subjected to single-cell RNA sequencing (scRNAseq) will be performed.
2. Investigation on whether B cells in the tumor are suppressed by myeloid cells, and through which mechanisms. The student will take advantage of C57BL/6-derived melanoma tumor models injected into WT animals, to investigate the quantity and quality of immune infiltrate in primary tumors and in lung metastases.

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

Technical skills: the student will be trained to perform complex experiments with animal models, including viral infections and in vivo tumor analysis. The goal is to reach proficiency in handling model animal models, in performing basic molecular and cellular techniques, in using multicolor flow cytometry and analyses softwares like FlowJo, Imaris, Prism.

Critical thinking skills: performing the proposed project will increase the student's knowledge in immunology and will help developing her/his critical thinking, as well as pushing the student to elaborate new ideas and biological questions.

References (max. 15)

1. S. Sammicheli, M. Kuka, P. Di Lucia, N. J. de Oya, M. De Giovanni, J. Fioravanti, C. Cristofani, C. G. Maganuco, B. Fallet, L. Ganzer, L. Sironi, M. Mainetti, R. Ostuni, K. Larimore, P. D. Greenberg, J. C. de la Torre, L. G. Guidotti, M. Iannacone. Inflammatory monocytes hinder antiviral B cell responses. 2016. Sci Immunol
2. E. Sala, M. Kuka. The Suppressive Attitude of Inflammatory Monocytes in Antiviral Antibody Responses. 2020. Viral Immunol
3. W. H. Fridman, F. Petitprez, M. Meylan, T. W.-W. Chen, C.-M. Sun, L. T. Roumenina, C. Sautès-Fridman. B cells and cancer: To B or not to B. 2021. Journal of Experimental Medicine