PROJECT 1

DoS: Mirela Kuka

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

Curriculum: Basic and Applied Immunology and Oncology

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 are an extremely heterogeneous and plastic cell type, and undergo several phenotypic changes when exposed to a certain cytokine-rich milieu within tissues. 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 by combining animal models, flow cytometry, scRNAseq, and fluorescence imaging:

1. To characterize the phenotype of myeloid cells interacting with virus-specific B cells
2. To analyze changes in B cell biology upon suppression by myeloid cells
3. To investigate whether B cells in the tumor are suppressed by myeloid cells, and through which mechanisms

Skills to be acquired by the student:

Technical skills: the student will be trained to perform complex experiments with animal models, including viral infections and in vivo tumor analysis. In a few months' time the student will be fully proficient in handling model animal models, in performing basic molecular and cellular techniques, in using multicolor flow cytometry and advanced imaging techniques, in using analyses softwares like FlowJo, Imaris, Prism.

Critical thinking skills: the student will increase her/his knowledge in immunology by studying several biological features of both monocytes and B lymphocytes. Application of this knowledge to the characterization monocyte-B cell interactions in the context of tumors will help developing her/his critical thinking, as well as pushing the student to elaborate new ideas and biological questions.

Communication skills: the student will learn to present data in a clear and organized manner during monthly progress reports. She/he will also learn to critically analyze other peer's data by participating to institutional seminars and journal clubs. The student will have the possibility participate to national and international meetings in order to present data obtained from this project.

References (max. 3)

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