PROJECT 1

DoS: Marta Muzio

Title: Exploring NFKBIZ-centered pathways in normal and malignant B-cells

Curriculum: BAIO

Link to OSR/UniSR personal page:
https://research.hsr.it/en/divisions/experimental-oncology/cell-signaling.html

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

Toll-like receptors (TLR) are key regulators of innate immunity; moreover, they bridge the innate and the adaptive immune responses by acting as co-stimulatory signals for B-lymphocytes. TLR are expressed both by normal and malignant B cells with a certain degree of specificity; however, the role of TLR in B cell lymphoid tumors and chronic lymphocytic leukemia (CLL) is not completely understood. We previously showed that TLR stimulation *in vitro* can activate several signaling pathways in malignant B-lymphocytes isolated from CLL or Lymphoma patients and can protect cells from spontaneous and/or drug induced apoptosis. Nevertheless, heterogeneity of response to TLR stimulation was observed between normal and malignant B-cells, and among different CLL cases, but the molecular basis for this heterogeneity is ill defined. We recently characterized distinct microRNAs, cytokines and the atypical NFKBIZ transcription factor as markers of TLR activation in specific CLL cases (1-2). The aim of this PhD project is to comprehensively characterize the molecular framework of TLR signaling molecules, with particular emphasis on the role of NFKBIZ, in normal and malignant B-cells.

To achieve this, we will:

1. Address how NFKBIZ is differentially expressed and regulated in normal B-cells and in CLL.

2. Dissect the molecular functions of NFKBIZ in B-cells, and their pathogenic effects in CLL, in the modulation of NFKB signaling pathways, gene expression and metabolic activation.

3. Identify drugs/molecules that can interfere with the NFKBIZ pathway to treat CLL.

Molecular, genetic and biochemical techniques will be applied *in vitro* and *in vivo* in murine models. The use of drug inhibitors will complement this translational study (3)

Skills to be acquired by the student:

Cellular and molecular biology techniques including genomics and transcriptomics (gene editing, ChIP-seq and RNA-seq).

Independent critical thinking; experimental planning and design; data analysis and data/progress reports; seminar presentations to the scientific community.

References (max. 3)

1) Toll-like receptor stimulation in splenic marginal zone lymphoma can modulate cell signaling, activation and proliferation. Fonte E, Agathangelidis A, Reverberi D, Ntoufa S, Scarfò L, Ranghetti P, Cutrona G, Tedeschi A, Xochelli A, Caligaris-Cappio F, Ponzoni M, Belessi C, Davis Z, Piris MA, Oscier D, Ghia P, Stamatopoulos K, Muzio M. Haematologica. 2015 Nov;100(11):1460-8.

2) Toll-like receptor 9 stimulation can induce IκBζ expression and IgM secretion in chronic lymphocytic leukemia cells. Fonte E, Vilia MG, Reverberi D, Sana I, Scarfò L, Ranghetti P, Orfanelli U, Cenci S, Cutrona G, Ghia P, Muzio M. Haematologica. 2017 Nov;102(11):1901-1912.

3) Interleukin-1 receptor-associated kinase 4 inhibitor interrupts toll-like receptor signalling and sensitizes chronic lymphocytic leukaemia cells to apoptosis. Delvecchio VS, Sana I, Mantione ME, Vilia MG, Ranghetti P, Rovida A, Angelillo P, Scarfò L, Ghia P, Muzio M. Br J Haematol. 2020 Feb 14.