PROJECT

Supervisor:	Marta Muzio
Title:	Understanding Toll-like receptor 10 function in B-cell lymphomas
Curriculum:	BAIO

Link to the personal page of the University or relevant hospital site website: https://research.hsr.it/en/divisions/experimental-oncology/cell-signaling.html

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Distinct Toll-like receptors (TLR) recognize different pathogen associated molecular patterns and/or endogenous danger signals and eventually trigger an innate immune response by activating inflammatory pathways; the analysis of mice lacking each TLR was instrumental for the identification of their specific functional role (1,2). However, TLR10 gene is not functional in mice, and no unique ligand/s and function/s have been agreed for this receptor (3). TLR10 expression is enriched in the B-cell compartment including B-cell tumors (2,4); nevertheless, the functional role and ligands specificity of TLR10 in B-cell lymphomas is unknown.

Rationale and hypothesis

We hypothesize that human TLR10 has a unique and novel function in the B-cell compartment, and that TLR10 expression in B-cell lymphoma can favor tumor growth.

Objectives and specific aims

The aim of this project is twofold: on the one hand, we will fill a gap of knowledge in immunology exploring the role of TLR10. On the other hand, we will exploit the exquisite selectivity of expression of TLR10 in the B-cell compartment to evaluate its role in B-cell tumors, with the future goal of designing innovative targeting approaches.

Specific objectives are:

1) To define the expression pattern and regulation of TLR10 in B-cell lymphomas. B-cell lymphoma cell lines, primary tumor cells from lymphoma patients, and B-lymphocytes from healthy donors will be analyzed.

2) To dissect the functional activity of TLR10 in terms of ligand binding, signaling capacity and impact on tumor cell biology. To identify TLR10 ligands, we will screen for specific binding molecules using different arrays. TLR10 signaling complex and downstream pathways will be analyzed in cell lines in which TLR10 is genetically inactivated or overexpressed.

Expected outcomes

The results of this project will elucidate the role of TLR10 in B-cell lymphomas and will help to define novel putative markers and/or targets that can be potentially exploited in other B-cell mediated diseases.

Skills that the student should acquire (max. 600 characters including spaces):

Cellular and molecular biology techniques including proteomics, genomics and transcriptomics (gene editing, CUT&Tag and RNA-seq).

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

References (max. 15)

1) **Decoding Toll-like receptors: Recent insights and perspectives in innate immunity**. Kawai T, Ikegawa M, Ori D, Akira S. Immunity. 2024 Apr 9;57(4):649-673.

2) **Toll-like receptors signaling: A complex network for NF-κB activation in B-cell lymphoid malignancies.** Ntoufa S, Vilia MG, Stamatopoulos K, Ghia P, Muzio M. Semin Cancer Biol. 2016 Aug;39:15-25.

3) **TLR10: An Intriguing Toll-Like Receptor with Many Unanswered Questions**. Rodrigues CR, Balachandran Y, Aulakh GK, Singh B. J Innate Immun. 2024;16(1):96-104.

4) **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.