Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2017-2018

Project Nº 4

Title: Functional characterization of constitutive B-cell receptor (BCR) and MYD88 signaling activation in lymphomagenesis

Department/ Laboratory: Laboratory of lymphoproliferative disorders. Division of Hematological Oncology. Center for Applied Medical Research (CIMA).

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Summary

Marginal-zone B-cell lymphomas (MZL) account for 10% of all human lymphomas. MZL are universally characterized by abnormal B-cell receptor (BCR) signaling activation as a consequence of cell-intrinsic and extrinsic abnormalities. Our laboratory has recently shown that the homeobox NKX2-3 transcription factor is abnormally expressed in tumor cells from patients with MZL, but not with other B-cell lymphomas. To determine the role of NKX2-3 in lymphomagenesis, we generated transgenic mice with selective expression of NKX2-3 in B cells. These mice showed progressive marginal-zone B-cell expansion that led to the development of tumors, faithfully recapitulating the principal clinical and biological features of human MZL. Mechanistically, NKX2-3 induced BCR signaling by phosphorylating Lyn and Syk kinases, which eventually drove malignant transformation (Robles et al, Nature Comm 2016).

In the current proposal we will continue deciphering the functional role of NKX2-3/BCR activation in MZL in cooperation with a constitutive MYD88 mutation commonly detected in patients with these lymphomas. To this end we have crossed Eμ-NKX2-3 mice with the MYD88-p.L252P transgenic mice, obtained through a scientific collaboration with Prof. Reinhardt (Knittel et al, Blood 2016). The different mutant and control mouse cohorts will be monitored for tumor development using procedures that have been set up in our laboratory (see Robles, Nat Comm 2016; Sagardoy, Blood 2013; Vicente-Dueñas, PNAS 2012; and Beltran, PNAS 2011). In parallel, analyses of primary samples from patients with MZLs will be conducted, aiming to determine whether mice develop human-like disease. Finally, transgenic mice will be used as tools for therapeutic testing in vivo, and responses to drugs in clinical use or development in patients with MZL (rituximab, ibrutinib, lenalidomide, anti-PD1/PDL1) will be evaluated. These data will allow to expand our knowledge about MZL biology and to define the optimal therapy in mice to be eventually translated into a clinical trial in patients with MZL.

References

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