Research Project Proposal
Academic year 2019-2020

Project Nº 33 ASIGNADO

Title: *Development of new combined therapies in acute myeloid leukemia. Towards a personalized treatment in patients with mutations in the FLT3 tyrosine kinase receptor and overexpression of the SET oncoprotein.*

Department/ Laboratory:
Department of Biochemistry and Genetics, School of Science, and Laboratory of Acute Leukemias, Hemato-oncology Program (CIMA), University of Navarra.

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Summary

Acute myeloid leukemia (AML) is an aggressive disease characterized by multiple genetic and epigenetic aberrations. Internal tandem duplication (ITD) of the juxtamembrane domain of the FLT3 receptor (FLT3-ITD) is the most prevalent mutation, accounting for ~25% of AML cases. This mutation results in ligand-independent constitutive activation of the receptor and impaired trafficking in compartments of the endomembrane system, such as the endoplasmic reticulum (ER), activating aberrant signaling pathways. Our group has reported that the oncoprotein SET, an endogenous inhibitor of the tumor suppressor phosphatase PP2A, is overexpressed in 30% of AML patients. Our preliminary results show that in AML cells with SET overexpression, SET presents a perinuclear half-moon pattern associated with the ER. Interesting, FLT3-ITD is associated with activation of the UPR.
HYPOTHESIS: SET overexpression could be involved in the UPR activation, cooperating with FLT3-ITD, in AML cells.
OBJECTIVES: (1) To investigate the localization of FLT3 and SET in AML cell lines with and without FLT3-ITD by immunofluorescence, using confocal microscopy. (2) To analyze the pathways regulated by wild type FLT3 and FLT3-ITD in AML, and to investigate their relationship with PP2A downstream targets. (3) To determine the effects of tunicamycin and brefeldin-A (UPR inductors), FTY720 (PP2A activator) and CX-4945 (a CK2 inhibitor that retains SET in the nucleus), in the localization of these proteins and in cell viability. (4) To determine the efficacy of combined treatments which modulate SET localization, reactivating PP2A, with FLT3 inhibition and UPR induction in the viability of AML cells in vitro and in vivo.

yes	**x**	**Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?**