Research Project Proposal
Academic year 2020-2021
Máster en Investigación Biomédica

Project Nº 31

Title: *Contribution of altered transcrtiptional regulators to the phenotype of Myelodysplastic Syndromes and Acute Myeloid Leukemia*

Department/ Laboratory *Myeloid Malignancies, Laboratory 1.04, Hem-Oncology Program, CIMA Universidad de Navarra*

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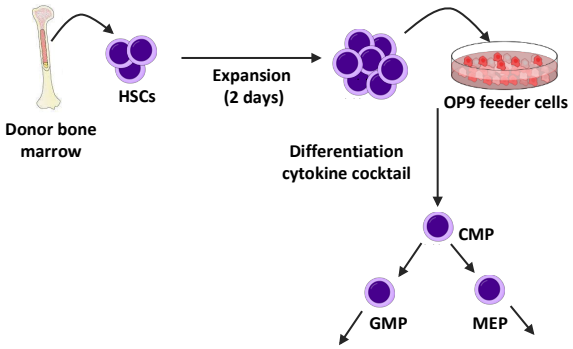
Summary

Myelodysplastic syndromes (MDS) represent hematological malignancies characterized by alterations in the differentiation and proliferation of hematopoietic progenitor cells. This is an age-related disease whose patients show increased risk of progression to acute myeloid leukemia (AML), a very deadly disease. Our group has performed a transcriptional study of hematopoietic stem cells (HSCs), determining how the expression of many genes is altered following different patterns of deregulation in aging and in the progression to MDS. These patterns have revealed how a group of chromatin and transcriptional regulators are overexpressed exclusively in the transition from elderly to MDS-associated cells, suggesting that they could be involved in the development of the disease. Our group has already studied one of these regulators, the transcription factor DDIT3, observing how its overexpression is able to promote a defect of normal hematopoietic differentiation. Nevertheless, the role or other candidates that show overexpression in a high percentage of MDS patients still needs to be elucidated.



FMyeloid-erythroid ex-vivo differentiation system from HSCs Workflow schematic: HSCs from healthy donors are expanded for 2 days, and later incubated over feeder cells in the presence of a cytokine cocktail that will promote the differentiation into different progenitor cells.

The aim of the present project is to determine the role of one of these candidate genes in the phenotype of MDS. To do this, the candidate will use an ex-vivo myeloid differentiation system starting from primary cells (HSCs from healthy donors). This system allows us to model early stages of hematopoietic differentiation in vitro, where the expression of specific genes can be manipulated. The candidate will generate lentiviruses to overexpress the factor of interest and use the differentiation system and flow cytometry analyses to evaluate the effect of the upregulation of the factor on normal hematopoietic differentiation. Furthermore, to determine the transcriptional lesions promoted by the upregulation of the factor, the candidate will perform RNA-seq analyses upon its exogenous overexpression in primary cells.

All in all, the candidate will acquire the following expertise:

- Human hematopoiesis cell biology.
- HSCs isolation, differentiation and culture.
- Ex-vivo myeloid differentiation system.
- Cloning and production of lentiviruses.
- Flow cytometry analyses of hematopoietic differentiation.
- Transcritptome profiling by RNA-seq analyses.

yes		**Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?**
no	**x**	