Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Studying the role of HOXA9 in IL7R-mediated B-cell leukemogenesis

Synopsis:

Acute lymphoblastic leukemia (ALL) is the most frequent cancer in pediatric patients, being characterized by abnormal proliferation of immature lymphoid cells which initiates in the bone marrow and can evolve to extramedullary sites. Around 85% of the children with ALL present with a B-cell phenotype (B-ALL). Interleukin-7 (IL-7) is a cytokine with vital importance in B and T cell development. The IL-7 receptor (IL-7R) is composed by the α and γc chain and IL-7/IL-7R signaling activates the JAK/STAT, MEK/ERK and PI3K/Akt pathways, which play a key role in maintaining cell viability and cell cycle progression. Our laboratory discovered a gain-of-function mutation in IL7R (encoding IL-7Rα) exon 6 (Nature Genetics 2011; Nature Immunology 2019) in T-ALL patients, which others found to extend also to B-ALL (J Exp Med 2011). More recently, we demonstrated that lymphoid-restricted mutant IL7R, expressed at physiological levels in conditional knock-in mice, establishes a pre-leukemia stage in which B-cell precursors display self-renewal ability, initiating B-ALL that resembles PAX5 P80R or Ph-like human leukemia (manuscript under revision).
HOXA family genes are known to be upregulated in specific T- and B-ALL subtypes, and HOXA9 leads to lymphoid leukemia in mice and acts as an oncogene in T-ALL and MLL-rearranged B-ALL. However, the role that HOXA9 plays in the context of IL-7R-mediated B-ALL development remains unaddressed.
In the current project we aim to: 1) determine the functional impact of HOXA9 modulation on B-cell leukemogenesis; 2) evaluate epigenetic mechanisms that may be involved in HOXA9 regulation in IL-7R-mediated B-ALL; 3) (if time allows it) identify gene expression alterations mediated by HOXA9 modulation in IL-7R-dependent B-ALL cells.
These tasks will involve using samples from our unique mouse model, genetically manipulating Hoxa9 levels by retroviral transduction, mouse transplantation experiments, in vitro culturing of leukemic cells with pharmacological inhibitors of histone deacetylases and DNA methyltransferases, flow cytometry analysis, immunoblotting, quantitative RT-PCR, and bulk RNA sequencing.

We are looking for a high quality, highly motivated student, with a positive and pro-active attitude to explore this exciting research avenue further. The student selected for this project will perform each of the above tasks (with the direct supervision of more experienced researchers in the lab), learn various state of the art techniques, and will be part of a vibrant research environment. The project will start in September (with the possibility of initiating earlier).

If you want to apply, please send an email with CV and motivation letter to: joao_barata@medicina.ulisboa.pt with cc to: diana.vaz@medicina.ulisboa.pt.

Applications are open until May 15th or until an appropriate candidate is selected.

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Webpage of the group