Research Project Proposal
Academic year 2019-2020

Project Nº 05

Title: *Role of clonal hematopoiesis of indeterminate potential (CHIP) in the pathogenesis and evolution of chronic pulmonary diseases.*

Department/ Laboratory: *CIMA, Laboratory 1.02; Regenerative Medicine and Hematology-Oncology Departments. Schools of Sciences and Medical School.*

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Summary With the advent of deep sequencing technologies, it has become apparent that a significant proportion of the healthy population carries somatic mutations in their hematopoietic stem cells leading to a clonal expansion of hematopoiesis, a condition known as CHIP (clonal hematopoiesis of indeterminate potential). CHIP's prevalence increases with age and can affect as many as 30% of the elderly population. In large cohorts of patients CHIP has been associated with an increased risk of developing hematological malignancies but also increased all-cause mortality. Functional studies using preclinical CHIP models have now demonstrated that mutant circulating leukocytes possess a pro-inflammatory phenotype that contributes to the exacerbations of cardiovascular diseases such as atherosclerosis or the resolution of myocardial infarction (MI). Chronic pulmonary diseases (CPDs) like COPD (Chronic Obstructive Pulmonary Disease), asthma and idiopathic pulmonary fibrosis are life-threatening conditions associated with ageing. Most importantly, persistent inflammation is a hallmark in the pathogenesis of CPDs. However, the implication of CHIP in the development, progression and resolution of chronic pulmonary diseases is completely unknown. Here we propose to evaluate the role of CHIP in the development and exacerbation of a COPD model in the mouse. We will model CHIP using genetic engineered mice designed to mimic Tet2 or Asxl1 loss-of -function or the P95H mutation in Srsf2 genes (some of the most commonly mutated genes in CHIP). Development and exacerbation of COPD in the context of CHIP will be evaluated by histological and advance imaging technologies such as microCT, multiparametric flow cytometry quantification and characterization of the immune infiltrate and high-throughput mRNA sequencing technologies.

yes	×
no	

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