Research Project Proposal
Academic year 2018-2019

Project Nº 45

Title: Age related clonal hematopoiesis role in thrombotic cardiovascular disease

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Summary Age-related mutations occur in hematopoietic stem and progenitor cells (HSPCs). These mutations can confer some evolutionary advantage to these cells and select for specific clones (1). Age-related clonal hematopoiesis (ARCH) is defined as the gradual, clonal expansion of HSPCs carrying specific, disruptive, and recurrent genetic variants, in individuals without clear diagnosis of hematological malignancies. However, ARCH dramatically increases the risk of future leukemia (2). Recently, ARCH has also been associated with general cancer mortality and, surprisingly, with vascular diseases (3,4), probably by activating chronic inflammation (5). However, the relationship between ARCH and thrombosis/embolism (the third more deleterious cardiovascular disease) is unknown.

The aim of is project is to study the presence of ARCH in patients with thrombotic diseases and healthy controls using next generation sequencing to stablish a relationship between ARCH and thrombosis. We will also study the role of a particular mutation (affecting the *TET-2* gen) using a model or murine ARCH (5). This model is prepared by bone marrow transplantation from animal with *TET-2* mutation into wild-type animals treated with radiotherapy. Animals with ARCH and wild-type ones will be submitted to a three different thrombosis model to assess the possible active role of ARCH on thrombosis development (6). We hope to set the basis to treating or even preventing ARCH to treat serious cardiovascular (and cancerous) diseases in humans.

(**1**) Xie M et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014;20:1472-8.
(**2**) Genovese G, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371:2477-87.
(**3**) Jaiswal S,et aal. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371:2488-98.
(**4**) Jaiswal S et al. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. N Engl J Med. 2017;377:111-121.
(**5**) Fuster JJ, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science 2017;355:842-847.
(**6**) Allende M et al. Hsp70 protects from stroke in atrial fibrillation patients by preventing thrombosis without increased bleeding risk. Cardiovasc Res 2016;110:309-18.

yes	**X**
no	

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