ImmunoTools *special* Award 2018

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Fra-2/stroma/inflammation axis in Systemic Sclerosis: a better understanding for developing new pharmaceutical targets

Background

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by microvascular damage, dysregulation of the immune system and generalized fibrosis in the skin and multiple internal organs. Fibrosis is associated with extensive accumulation of extracellular matrix constituents by myofibroblasts, contractile cells that express alpha smooth muscle actin. Cardiac involvement in SSc is a major negative prognostic factor. However, the origin of cardiac myofibroblasts remains unknown. Both stromal cells and bone marrow derived cells contribute to the myofibroblast pool in SSc. In this project, the Fos-related antigen 2 (Fra-2) tg mouse is used as SSc mouse model due to the development of inflammation, vasculopathy and fibrosis mainly in the skin and internal organs. In parallel, human cardiac fibroblasts and endomyocardial biopsies (EMBs) are being used for translating our research into human biology.

Objectives

The main goal of the project is to investigate the mechanisms involved in the differentiation into myofibroblast-like cells and the interaction between stroma and the immune system during myocardial fibrogenesis. In particular, we would like to study the Fra-2 tg mouse model to look into the stromal-to-myofibroblast differentiation, which might contribute to the fibrogenesis in an autocrine and paracrine manner, influencing also the differentiation of infiltrated bone marrow derived cells.

Project description

As a first step, we will characterize cytokines responsible for the systemic inflammation in the blood of Fra-2 tg mice. In addition, we will evaluate the composition of different immune cell types (monocytes, T- cells, granulocytes), both infiltrating the cardiac tissue and circulating in the blood stream. Moreover, we will

perform *in vitro* experiments for evaluating the cytokine composition of supernatants from different cultured stromal cell subsets isolated from the heart of WT and Fra-2 mice. ImmunoTools ELISAs for murine IL-6, IL-17A and TNF-a would be used for this purpose. These experiments will allow us to determine the contribution of particular subsets of stromal cells to the inflammatory milieu of the cardiac tissue in SSc.

In parallel, we will perform experiments on serum samples collected from healthy controls (HC) and SSc patients: hFra-2 overexpression will be performed in human cardiac fibroblasts. Subsequently, we will culture them with medium enriched by serum from HC and SSc patients in order to assess the effect of Fra-2 overexpression together with inflammation on the differentiation capacity of stromal cells. This set-up will help us to better understand the role of the axis Fra-2/stromal expansion/inflammation.

Last, but not least, we will evaluate the presence of committed stromal cell progenitors in Endomyocardial Biopsies (EMBs) co-expressing fibrotic markers such as collagen 1a1, fibronectin and periostin.

Significance of the project

The role of inflammation and the contribution of the stromal compartment in the fibrogenesis of SSc is still poorly understood. Our research will give better insights into the molecular mechanisms responsible for the onset and progression of the disease. The use of both animal models and patients' derived material represents a good strategy for the development of new, effective pharmaceutical targets. During this project, the FACS antibodies and ELISA from ImmunoTools will be used in all in vitro experiments in order to better phenotype the cellular composition of immune cells during inflammation in SSc.

ImmunoTools *special* AWARD for **Mara Stellato** includes 25 reagents

FITC - conjugated anti-mouse CD3e

PE - conjugated anti-mouse CD4

APC - conjugated anti-mouse CD11b, Gr-1, NK-cells

mouse ELISA-set: mouse IL-6, mouse IL-17A, mouse TNF-a

human ELISA-set: human IL-1beta, human IL-6

DETAILS more AWARDS