Fundació La Marató de TV3
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Heart diseases

DILATATION OF THE ASCENDANT AORTA AND CORONARY ANEURISMS IN PATIENTS WITH SYSTEMIC VASCULITIS (GIANT CELL ARTERITIS AND KAWASAKI DISEASE). ROLE OF THE HIF PATHWAY IN VASCULAR REMODELLING/INFLAMMATION

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1. Summary

General Objectives

To investigate new molecular pathways associated with the development of dilatation of the ascendant aorta in patients with giant cell arteritis (GCA) and of coronary aneurisms in patients with Kawasaki disease (KD). To evaluate the role of HIF–mediated signalling in the evolution of these vascular and inflammatory lesions in these patients starting from the experimental observations in a genetic model of KD with activation of the HIF pathway that develops coronary aneurisms and systemic inflammation.

Specific objectives

1. To identify new parameters associated with the development of aortic dilatation, including demographic data, cardiovascular risk factors, concomitant medication, clinical manifestations and evolution of the disease.

2. To characterise physiopathological cardiovascular aspects in GCA patients and the animal model of KD and to evaluate its relationship with cardiovascular complications:

2.1. To analyse the vascular architecture assessing the degree of hypoxia, fibrosis, proliferation of the neointima/adventitia, content of vascular smooth muscle cells (VSMC) and breakage of elastic fibres using specific staining in inflammatory lesions of temporal artery of patients with GCA and coronary arteries of the mouse model of KD.

2.2. To investigate the vascular remodelling mechanisms analysing the expression of metalloproteases with elastolytic activity, their inhibitors and fibrogenic pathways in biopsies of temporal arteries of patients with GCA, primary cultures of VSMC of patients with GCA and arteries of the mouse model of KD.

2.3. To evaluate the activation of the HIF pathway in the vasculature and determine the degree neovascularisation in inflammatory lesions of temporal arteries of patients with GCA and coronary arteries of the mouse model of KD.

2.4. To generate a gene expression profile in cultures primary of VSMC of patients with GCA with or without aortic dilatation.

3. To study systemic inflammation in patients with KD and GCA and the animal model of KD.

3.1. To analyse the adaptive immune response (subgroups of T helper, Treg, B and NK cells) in blood, lymphoid organs and infiltrate in tissue (myocardium and coronary arteries) in murine model of KD. Analysis of the Th1, Th2, Th17 and Treg populations in blood of patients with KD and tissues implicated in patients with GCA and model of KD.

3.2. To determine miRNA profiles in proinflammatory Th17 cells compared with Treg cells in patients with KD and in serum/plasma of patients with KD and GCA. To evaluate les differential expressions of miRNA as biomarkers with diagnostic potential.

4. To analyse by directed sequencing of new variants of genes of the hypoxia pathway (vhl, phds, hifs) associated with formation of aneurism in patients with GCA and KD.

Summary of the experimental design and methodology

Immunopathologic studies of tissues of patients with GCA with and without aneurisms and tissues of the murine model of KD. Gene expression profile of VSMC isolated from arteries of patients with GCA with and without aneurisms. Evaluation by directed sequencing of new variants of the genes phds/vhl/hifs and their association with adverse vascular evolution in patients with GCA and KD. Analysis of systemic inflammation, in particular of the imbalance in the Th17/Treg populations in issue of patients with GCA, animal model of KD and peripheral blood of patients of KD. Generation of a transcriptional profile of miRNA in serum of patients with GCA and KD.

Synthesis of the original work plan

Between the first and second years the samples of GCA and KD patients will be recruited and Dr Cid's team will perform the study of clinical parameters of development of aortic dilatation in patients with GCA. Also, both research groups will

characterise the vascular and inflammatory alterations in samples of patients with GCA and KD, as well as in the mouse model of KD in Dr Martín Puig's group. A particular analysis will be made of the architecture of the arteries, the vascular remodelling mechanisms and the state of activation of the HIF signalling pathway in these samples. Dr Cid's team will also perform a transcriptional profile in primary culture samples of vascular smooth muscle cells of arteries from patients with GCA with and without dilatation. Also, there will be an analysis of the immune response in lymphatic organs and cardiovascular tissues in the murine model of KD and also in blood of samples of patients with GCA and KD. A transcriptional profile will be generated of miRNA in patients with GCA and KD and with evaluation of their potential use as diagnostic biomarkers. In the middle of the second year and first six months of the third there will be the sequencing and bioinformatic analysis of possible new gene variants of elements of the hypoxia pathway in samples of patients with GCA and KD previously identified in the first year and a half of the project. As of the second half of the second year a start will be made on writing the manuscripts with the observations that have been made and the corresponding works will be sent for publication.