

**A novel non-hypoxic and sex-biased mechanism of HIF-1 $\alpha$  in human aortic valve interstitial cells: crosstalk between JAK-STAT and TLR pathways**

**Authors:**

I. Parra Izquierdo<sup>1</sup>, I. Castanos-Mollor<sup>1</sup>, J. Lopez<sup>2</sup>, C. Gomez<sup>1</sup>, A. San Roman<sup>2</sup>, M. Sanchez Crespo<sup>1</sup>, C. Garcia-Rodriguez<sup>1</sup>, <sup>1</sup>Instituto de Biología y Genética Molecular (CSIC-Universidad de Valladolid) - Valladolid - Spain, <sup>2</sup>ICICOR, CIBER de Enfermedades Cardiovasculares (CIBERCV), Hospital Clínico Universitario - Valladolid - Spain,

**Topic(s):**

Basic Science - Cardiac Diseases: Valvular Heart Disease

**Citation:**

European Heart Journal ( 2018 ) 39 ( Supplement ), 1098

**Funding Acknowledgements:**

Grants SAF2013-44521R; BIO/VA36/15, GRS 1432/A/16, CSI035P17; PI14/00022 and CIBERCV; Fund Domingo Martínez. Fellowships from UVa and CyL government.

**Introduction:** Immune cell infiltration is one of the earliest events in calcific aortic valve disease (CAVD). Recent data showed that infiltrated T lymphocytes secrete active interferon (IFN)- $\gamma$ , the effects of which in resident valve cells remain unknown. In addition, angiogenesis has been pointed out as a key player in CAVD since new vessels formation and hypoxia-inducible factor (HIF)-1 $\alpha$  have been detected in calcified aortic valves. However, its underlying molecular mechanisms are still poorly understood.

**Purpose:** To elucidate the role of IFN- $\gamma$  on inflammation, angiogenesis and calcification of human aortic valve interstitial cells (AVIC) isolated from male and female patients.

**Methods:** AVIC were isolated from healthy valves by collagenase digestion and exposed to IFN- $\gamma$  and/or lipopolysaccharide (LPS). Western Blot and ELISA were used to analyze pro-inflammatory and pro-angiogenic molecules. The osteogenic marker bone morphogenetic protein (BMP)-2 and the anti-angiogenic factor chondromodulin-1 (ChM-I) were analyzed by RT-qPCR. Immunofluorescence was used to evaluate HIF-1 $\alpha$  nuclear translocation. Alizarin red staining and calcium deposits quantitation were performed to evaluate in vitro calcification of AVIC in high-phosphate conditions.

**Results:** Data showed that IFN- $\gamma$  and LPS cooperated to promote nuclear factor (NF)- $\kappa$ B activation, and to induce adhesion molecule expression and interleukin (IL)-6 secretion. Moreover, IFN- $\gamma$  and LPS combination promoted the induction of HIF-1 $\alpha$  and the secretion of its target gene, vascular endothelial growth factor (VEGF)-A. The effect exhibited sex differences and was blocked with a HIF-1 $\alpha$  inhibitor. Additionally, a decrease of ChM-I expression was observed. AVIC morphology markedly changed upon long-term stimulation with IFN- $\gamma$ , exhibiting an osteogenic phenotype characterized by BMP-2 induction. Strikingly, marked sex differences were found in BMP-2 expression and IL-6 secretion. Finally, IFN- $\gamma$  promoted AVIC calcification that was further potentiated by LPS, being male AVIC more prone to calcification. Remarkably, pre-treatment with the JAK1/2 inhibitor ruxolitinib abrogated IFN- $\gamma$  effects.

**Conclusions:** IFN- $\gamma$  promotes pro-inflammatory, pro-angiogenic and pro-osteogenic responses in AVIC, which are potentiated by LPS in a sex-specific manner. Also, IFN- $\gamma$  combined with LPS induces HIF-1 $\alpha$  by a hypoxia-independent mechanism. Our results point to JAK-STAT pathways as potential therapeutic targets for CAVD.

This content is past the free consultation date... Get your access now

A novel non-hypoxic and sex-biased mechanism of HIF-1alpha in human aortic valve interstitial cells: crosstalk between JAK/STAT and TLR pathways

Session: Best Posters 6 (Congress/ESC-Congress-2018/Best-Posters-6-Best-Posters-in-Sex-and-gender-related-mechanisms-of-cardiovascular-diseases) | Speaker: Ivan Parra Izquierdo

Table with 2 columns: Abstract, Slides, Video, Report

Abstract: Authors: I. Parra Izquierdo, J. Castano-Molina, J. Lopez, C. Gomez, A. San Roman, M. Sanchez Crespo... Introduction: Immune cell infiltration is one of the earliest events in calcific aortic valve disease (CAVD)...

Other presentations from this session: Best Posters 6: Best Posters in Sex and gender-related mechanisms of cardiac diseases

Other presentations from this speaker: Ivan Parra Izquierdo, Spain

Based on your interests: Long-term risk of infective endocarditis following transcatheter aortic valve implantation: a nationwide cohort study

Three reasons why you should become a member: 1. Access your congress resources all year-round on the New ESC 365

Our sponsors: ESC 365 is supported by Bayer, Boehringer Ingelheim, Bristol-Myers Squibb and Pfizer Alliance, and Novartis Pharma AG.