NF-kappaB p65-Ser536 mediates lysophosphatidic acid-induced BMP-2 gene through Rho-kinase pathway: Role in Calcific aortic valve disease:

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Abstract

Introduction: Calcific aortic valve stenosis (CAVS) is the most frequent heart valve disorder. However, there is unfortunately no medical therapy able to stop or to slow the natural course of this disease. Studies indicate that mineralization of the aortic valve may be related to the inflammatory process. Recently, we documented that lysophosphatidic acid (LPA), which is generated by autotaxine (ATX), was present in the aortic valve and was an important driver of aortic valve mineralization.

Methods: By using different approaches we have investigated the effect of LPA on the osteogenic phenotype. We have also documented the mechanisms whereby the NF-κB pathway is activated by LPA and promotes the osteogenic transition of cells

Results: In cell culture we found that the expression of osteogenic genes (BMP2, RUNX2, BGLAP, and COL1A1), alkaline phosphatase (ALP) activity and valve interstitial cells (VICs) mineralization were increased by several-fold after a treatment of cells with LPA. Also, we have shown that LPA-induced osteogenic response relied on RhoA pathway downstream of the LPA receptor-1 (LPAR1). In this regard, we found that RhoA is a regulator of the NF-κB pathway and promotes BMP2 expression. In addition, by using promoter luciferase assay we documented that NF-κB-p65 phosphorylation on serine536 (p65 phospho S536) activates BMP2 promoter following a treatment with LPA. We next showed by using chromatin immunoprecipitation assays (ChIP) that the binding of p65 phospho S536 to BMP2 promoter is not reversed by the super repressor mutant IκBα SS32-36AA (IκBα-SR) overexpression.

Conclusion: LPA-induced VICs mineralization is dependent on p65 phosphorylated serine 536 pathway. Hence, we documented a novel mechanism whereby LPAR1 and RhoA modulate the NF-κB pathway and its downstream target BMP-2, which is a strong promoter of VICs mineralization and thus could represent a novel therapeutic target in CAVS.

Background

CAVS is a progressive and slow disease characterized by several processes essentially lipid retention, inflammation and fibro-calcic remodelling leading to alteration of valve mobility.

The retention of lipids such as Lp(a) and ox-LDL within the aortic valve may play a role in the pathobiology of CAVS.

The only effective treatment of the CAVS is: the replacement of the aortic valve.

Recently, we have documented that lysophosphatidic acid (LPA) was present in the aortic valve and plays an important role in aortic valve mineralization.

LPA receptors (LPARs) can be coupled to a wide variety of Gα proteins giving a wide variety of signaling cascades, which may have intricate relationships during the mineralization of VICs.

In the heart, LPAR1 and LPAR3 have been shown to be widely expressed and to mediate pro-atherosclerotic and pro-inflammatory effects.

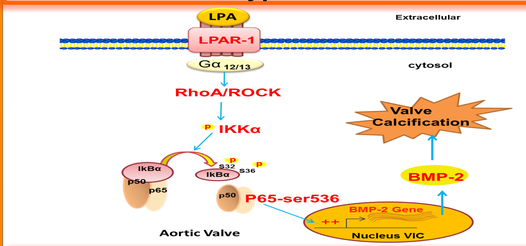
So far, the mechanism of action whereby LPA promotes mineralization of VICs remains unknown.

Recently, we identified that the NF-κB pathway is activated in human aortic valves and promoted the production of IL-6, which in turn entrained an osteogenic transdifferentiation of VICs

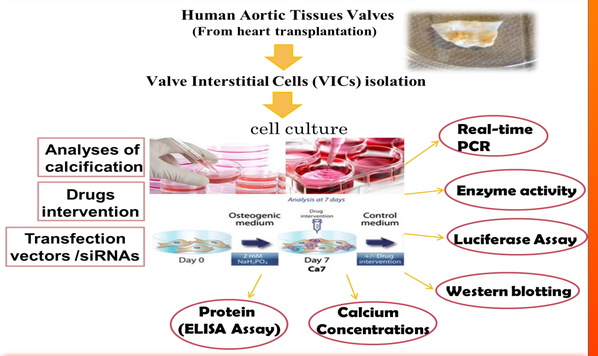
Objective

The aim of the study is to understand the mechanisms and signaling pathways by which LPA promotes inflammation and the mineralization of the aortic valve

Hypothesis



Methods



Results

Figure 1 : LPA induces an osteogenic response in VICs

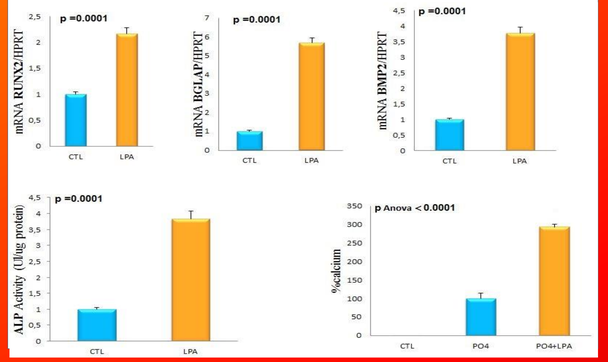


Figure 2: LPA induces osteogenic program through LPAR1and RhoA

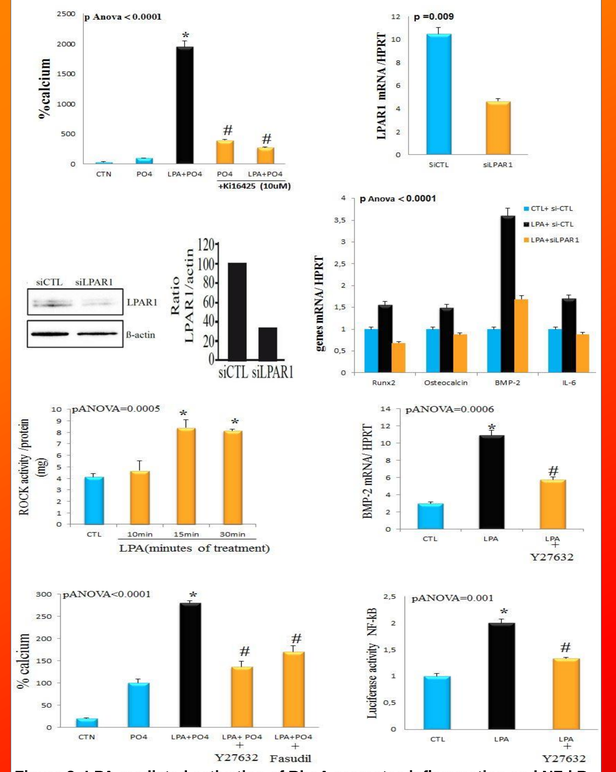


Figure 3 : LPA-mediated activation of RhoA promotes inflammation and NF-kB activity

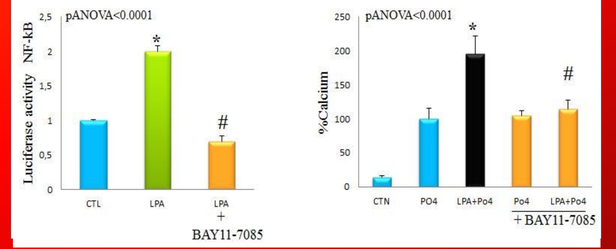


Figure 4 : LPA induced expression of BMP-2 is mediated by RhoA and NF-kB

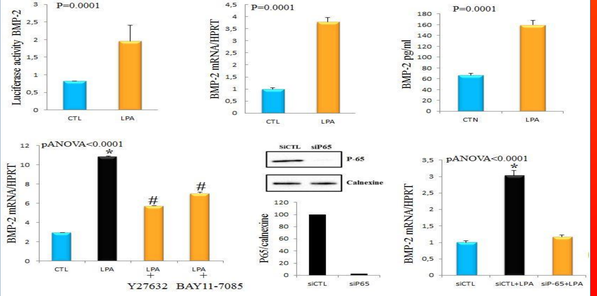
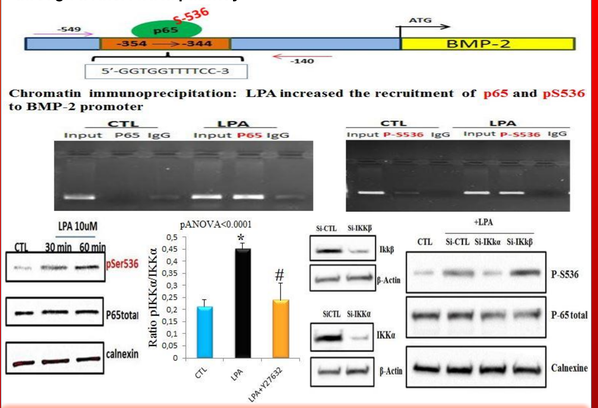


Figure 5 : Phosphorylated p65 Ser536 promotes BMP2 gene activation through a RhoA-IKKα pathway



Conclusion

This is the first study to report that LPA promotes the mineralization of VICs through a LPAR1-RhoA and NF-kB pathway and its downstream target BMP-2 .

We highlighted that LPA-induced VICs mineralization is dependent on p65 phosphorylated serine 536 pathway.

LPAR-1 and p65-ser536 could represent novel potential targets in the treatment of aortic stenosis .

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