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Inflammation-induced EndMT facilitates BMP-9-mediated vascular calcification in a BMP type II receptor (BMPR2) dependent manner

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Introduction

Vascular calcification is a common feature in many disorders, such as atherosclerosis, chronic kidney disease and hypertension. Our group, among others, has suggested that endothelial cells (ECs) can undergo Endothelial-to-mesenchymal transition (EndMT), leading to osteogenic cells, thereby contributing to vascular calcification. EndMT is modulated by several stimuli, including inflammation and Transforming growth factor (TGF)-β family members, such as the Bone morphogenetic proteins (BMPs). The mechanisms underlying EndMT in vascular calcification are not yet elucidated.

Objectives

-Test the interplay between inflammatory cytokines and TGF-β family members, to induce EndMT in primary human aortic endothelial cells (HAoECs).
-Investigate how EndMT affects BMP-induced mineralization in HAoECs.
-Determine the mechanisms by which EndMT modulates BMP-induced osteogenic response.

Material and Methods

In vitro cultures of primary human aortic endothelial cells (HAoECs) were used to investigate EndMT and mineralization in response to cytokines and growth factors. The murine immortalized EC line 2H11 was employed in biochemical studies. We used the ApoE*3Leiden mouse model of accelerated atherosclerosis and sections from human atherosclerotic donors for ex-vivo studies.

Statistics

Student’s t-test was used and P < 0.05 was considered significant. All experiments were performed at least 3 independent times. The results are shown as the mean ± SD of the mean of 3 independent experiments.

Results

We identified tumor necrosis factor (TNF)-a and interleukin (IL)-1β as potent inducers of EndMT that sensitize HAoECs for BMP-induced mineralization. Upon TNF-a stimulation, HAoECs potently down-regulate the
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Inflammation-induced EndMT facilitates BMP-9-mediated vascular calcification in a BMP type II receptor (BMPR2) dependent manner. BMPR2 down-regulation reduced the activation of JNK/c-jun, which potentiates EC mineralization. Finally, we found that endothelial cells undergo EndMT in the aorta of atheroprone ApoE*3Leiden mice and in human aortic sections, which correlates with decreased expression of BMPR2.

**Summary and conclusions**

We identified BMPR2 down-regulation as a key process in inflammation-induced EndMT and calcification. This highlights BMPR2 as a potential druggable target for calcification disorders and suggests BMPR2 monitoring as a biomarker for EndMT.