

C106. Role Of The MAPK/ERK Pathway In Valvular Interstitial Cell Calcification

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OBJECTIVES: Relatively little is known about the etiology of heart valve disease on the molecular level. The MAPK/ERK pathway has been linked to the expression of a contractile phenotype in valvular interstitial cells (VICs). However, a direct correlation between MAPK/ERK pathway activity and VIC calcification has not been previously described.

METHODS: The role of the MAPK pathway in the calcification of VIC cultures was investigated by measuring ERK activation in both calcifying and non-calcifying VIC environments, and then, conversely, analyzing the effects of ERK pathway inhibition on VIC calcification and phenotype. Alizarin Red S staining was performed to visualize and quantify the extent of culture calcification. The migration, proliferation, apoptosis and gene expression of VICs treated with the ERK inhibitor were also quantified.

RESULTS: Prolonged elevation of phosphorylated ERK 1/2 was found in calcifying VIC cultures, while directly blocking ERK signaling resulted in a dramatic decrease in nodule number, nodule size, and total calcified area. Inhibition of ERK pathway signaling was also associated with a dramatic decrease in apoptosis, which may have contributed to the decreased nodule formation obtained via ERK inhibition. Real-time PCR analysis revealed that calcified samples exhibited significantly elevated expression of several myofibroblastic and osteoblastic markers, while ERK inhibition substantially reduced the expression of these markers, often to levels comparable to the non-calcifying control.

CONCLUSIONS: These data suggest that the MAPK/ERK pathway plays an important role in regulating the phenotype and calcification of VICs, wherein sustained pathway activation is associated with increased VIC calcification.

Figure 1

