

C108. Pravastatin Inhibition Of Valvular Interstitial Cell Calcific Nodule Formation Is Mediated Through Prevention Of Myofibroblastic Differentiation

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OBJECTIVES: Calcific aortic is characterized by fibrosis and deposition of calcified tissue. Statins, have shown promise in prevention of calcification in cultured valvular interstitial cells (VICs), which spontaneously form multicellular aggregates that lead to excessively calcified tissue. The objective of this study was to investigate the mechanism of statin inhibition of VIC calcification.

METHODS: The process of nodule formation was observed through real-time microscopic tracking. Calcific nodules were stained and counted with TGF- β 1 and pravastatin treatment. siRNAs and overexpression plasmids were transfected into VICs to examine to effect of alpha smooth muscle actin (α SMA) knock-down and overexpression.

RESULTS: With real-time microscopic tracking, we observed that the confluent VIC monolayers spontaneously contract into rounded nodules, suggesting that myofibroblastic contractility is a critical step in the process of nodule formation. Indeed, knock-down of α SMA expression with siRNAs reduces nodule formation in VICs, suggesting that decreased levels of α SMA stress fibers prevents the contraction of VIC populations into pathological nodules. Conversely, over-expression of α SMA leads to increased nodule formation. Statin treatment of VICs also reduces α SMA expression and decreases nodule formation, leading us to investigate the link between statins and α SMA expression. Treatment with cholesterol biosynthesis intermediates and inhibitors indicates this action is mediated through HMG-CoA reductase inhibition and Rho kinase activity.

CONCLUSIONS: This work demonstrates that differentiation of fibroblast VICs into myofibroblasts is a critical step in the process of calcification. Further, statin inhibition of VIC calcification is attributed to inhibition of the increased α SMA expression that results upon myofibroblast activation.