Statin therapy transforms cardiac fibroblast function in human failing heart

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**PROBLEM**
The effect of statin therapy, a commonly used lipid lowering strategy in patients at risk for cardiovascular disorders, on cardiac fibroblast function is not known.

**BACKGROUND**
Cardiac fibrosis underlies in the progression of atrial fibration and heart failure. Fibroblast proliferation and differentiation precedes fibrosis. Statin (HMG-CoA (3-hydroxy-3-methylglutaryl-CoenzymeA) reductase inhibitor) therapy is recommended (by ACC/AHA) for patients having cardiovascular disease. Apart from the established lipid lowering effect, statins have other effects reported in animal models but its effect on human ventricular fibroblasts (HVF), responsible for extracellular matrix secretion and fibrosis, is unknown. As excessive fibrosis is associated with heart failure (HF) and fibroblast - myofibroblast trans-differentiation precedes fibrosis, we tested the hypothesis that statin therapy interferes with the normal proliferation and differentiation function of HVFs from HF patients.

**OBJECTIVE**
To determine the effect of statin therapy on cardiac fibroblasts, isolated from failing heart patients either under statin therapy or not, and to determine the signaling mechanisms involved in this effect.

**METHODS**
Cell Culture: Primary cultures of HV from HF patients undergoing ICD implantation under statin therapy (HF-Statin) for at least 1 year (n = 4) or not (n = 4), non-diseased HV from trauma victims (n = 3), were compared.

Proliferation assays: The fibroblast proliferation was assessed by 3H-ethyl-2-deoxyuridine (3H-EUD), a thymidine analogue, incorporation assay, and cell counts using hemocytometer.

Immunoblotting: Expression of a smooth muscle actin (α-SMA) and GAPDH was assessed in fibroblast culture lysate.

Immunohistochemistry: Myofibroblasts were identified with immunolocalization of α-SMA using appropriate primary/secondary antibodies, visualized under confocal microscopy and quantified using Fluoview software.

PCR Array: Transcriptoric changes were studied from total RNA using RT2 Profiler™ PCR array.

**RESULTS**

**STATIN THERAPY MITIGATES FIBROBLAST DIFFERENTIATION:**

**Fig. 1:** Representative western blotting images(top) of HV lysates probed for the expression of α-SMA. Failing heart HVs that were NOT under statin therapy showed significantly higher expression of α-SMA compared to the failing heart HVs that were under statin therapy for at least one year. Bar graph(bottom) displays the pooled average image densities of α-SMA bands normalized to the corresponding GAPDH bands. Bands were quantified using Image J software, *p = 0.03 vs Control, n=3* vs HF+Statin.

**Fig. 2:** Under confocal microscopy, immunolocalization showed significantly high population of myofibroblasts (α-SMA +) in the HF-No Statin group (middle) vs the control (left) or HF+Statin group (right), suggesting a statin-sensitive increased HFV differentiation.

**CONCLUSIONS**
Statin interferes in the human ventricular fibroblasts differentiation function by associated changes in the transcriptome and signaling molecules involved in fibrosis. This anti-fibrotic effect of statins may be harnessed in therapeutics to mitigate the progression of cardiac fibrosis and heart failure, apart from its lipid-lowering effect.