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 the progression of atrial fibrillation 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 - myocardial 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
Cells: Primary cultures of hVF from HF patients undergoing (VAD implantation under statin therapy (HF+Statin) for at least 1 year (n = 3) or not (n = 4), non-diseased hVF from trauma victims (n = 3), were compared.

Proliferation assays: The fibroblast proliferation was assessed by 5-ethyl-2-deoxyuridine (EdU), 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: Transcriptomic changes were studied from total RNA using RT2 Profiler™PCR array.

Aurora Antibody Array: Exploratory antibody array was performed by Full Moon Biosystems Inc.

Statistical Analysis: unpaired Student’s t-test or one-way ANOVA

RESULTS
STATIN THERAPY MITIGATES FIBROBLAST DIFFERENTIATION: Fig 1.

STATIN THERAPY DIFFERENTIATES MYOFIBROBLASTS TO FIBROBLASTS: Fig 4.

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.