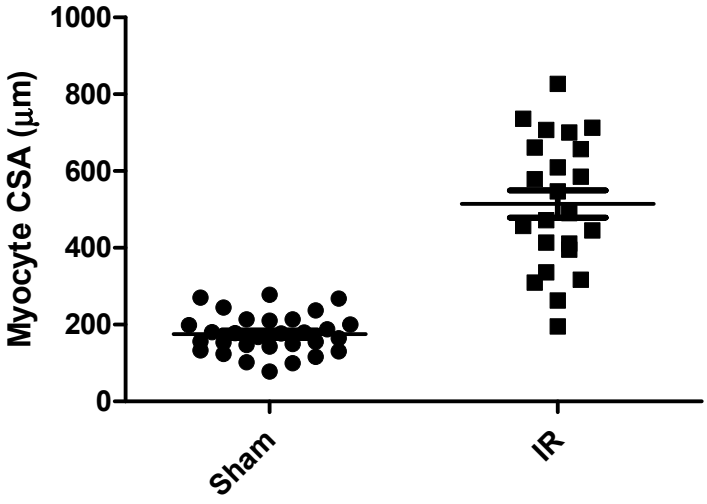
Supplemental methods

Calcium transients and sarcomere shortening:

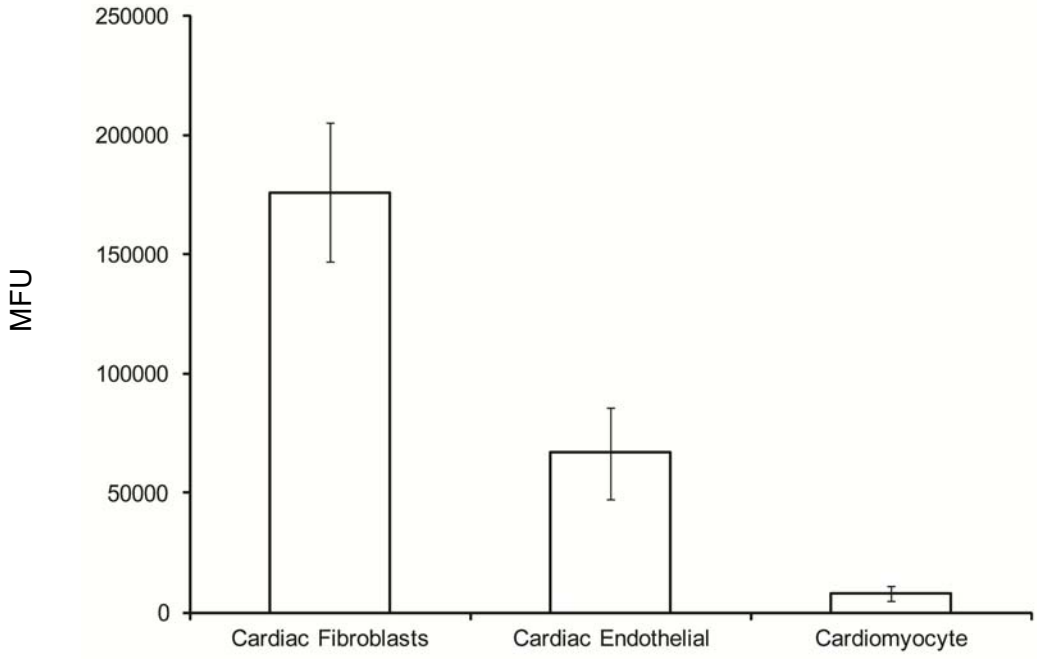
Cardiac myocytes were isolated as described[16]. Sarcomeric shortening and calcium transients were measured as described using simultaneously using Video - based sarcomere length and Ca acquisition module system (IonOptix, Milton, MA).

Cyokine analysis

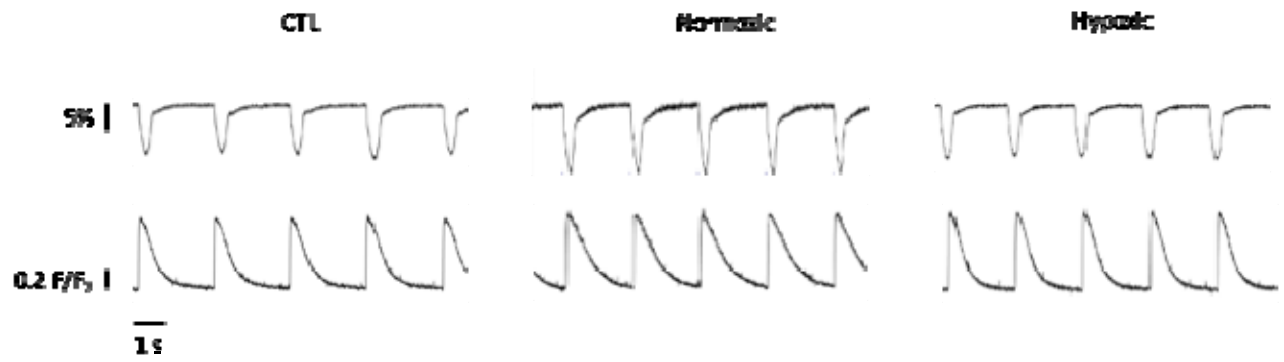
LV tissue (weighing about 100 mg) was rinsed quickly with HBSS, minced, homogenized, and incubated overnight in 1 mL NP-40 lysis buffer supplemented with protease inhibitor cocktail (Sigma). The suspensions were centrifuged and supernatants collected for further analysis. A bead-based multiplex assay (EMD Millipore RECYTMAG-65K) was used to measure levels of various proteins using manufacturer's instructions. Assay buffer was used as matrix solution. An ELISA kit was used for measuring IGF-1 levels (Ray Biotech ELR-IGF1-1) because of unavailability of that analyte on the multiplex assay. The obtained target protein concentration from each sample was normalized by its respective total protein concentration. Total protein concentrations were measured using manufacturer's protocol (NanoDrop 2000) based on absorbance at 280 nm. Data are expressed as pg/mg total protein.



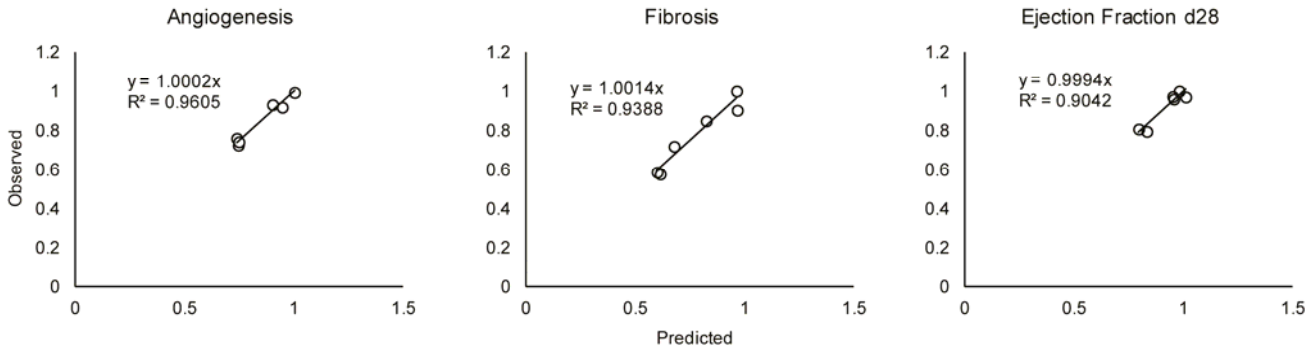
Supplemental Figure I. Sample histogram from hypertrophy measurements showing distribution of myocyte size (CSA=cross sectional area) from one sham and one IR treated animal.



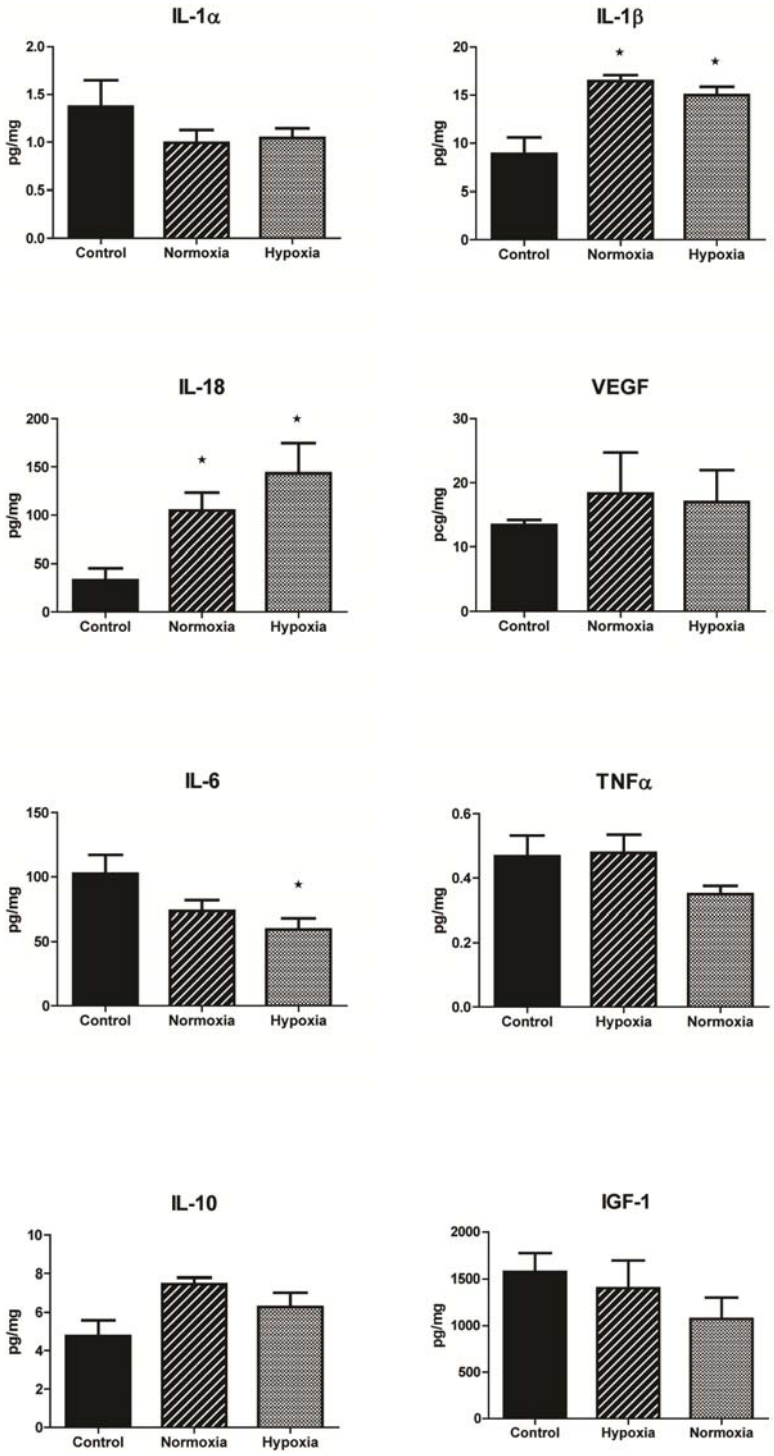
Supplemental Figure II: Exosomal uptake by various cardiac cell types. Figure demonstrates maximal uptake by cardiac fibroblast cells compared with endothelial and cardiomyocytes. Uptake is expressed as mean fluorescence units (MFU).



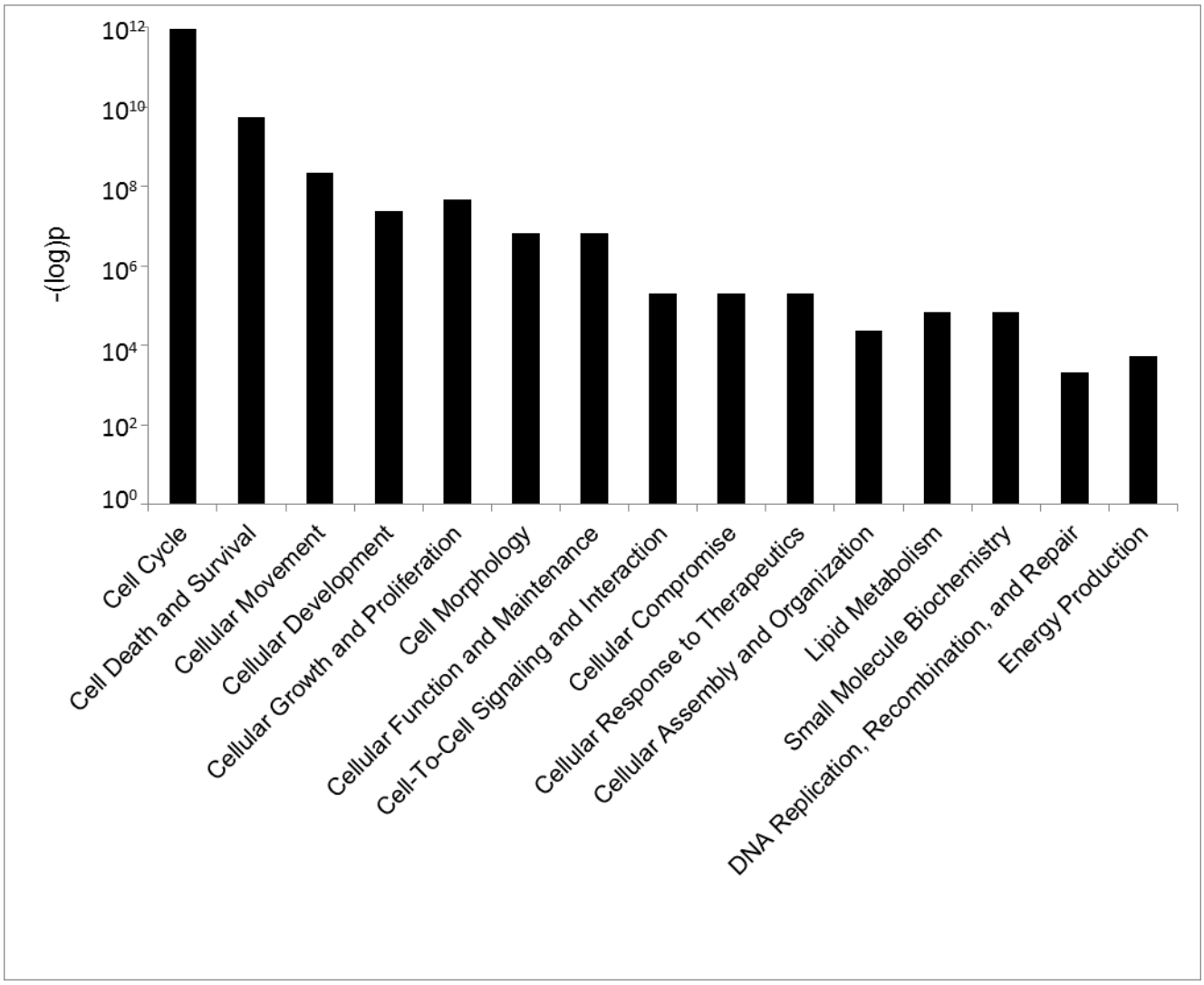
Supplemental Figure III: Sarcomere shortening and Ca transient amplitudes were recorded from rat ventricular myocytes loaded with 10 μM fluo-4/AM after 12 hr treatment with exosomes. (A) Example traces of percentage of sarcomere length shortening (top) and Ca transient recordings (bottom) from control and the various treatment groups. Summary data for sarcomere shortening (B) and Ca transient amplitude (C) (average±SEM; n=4).



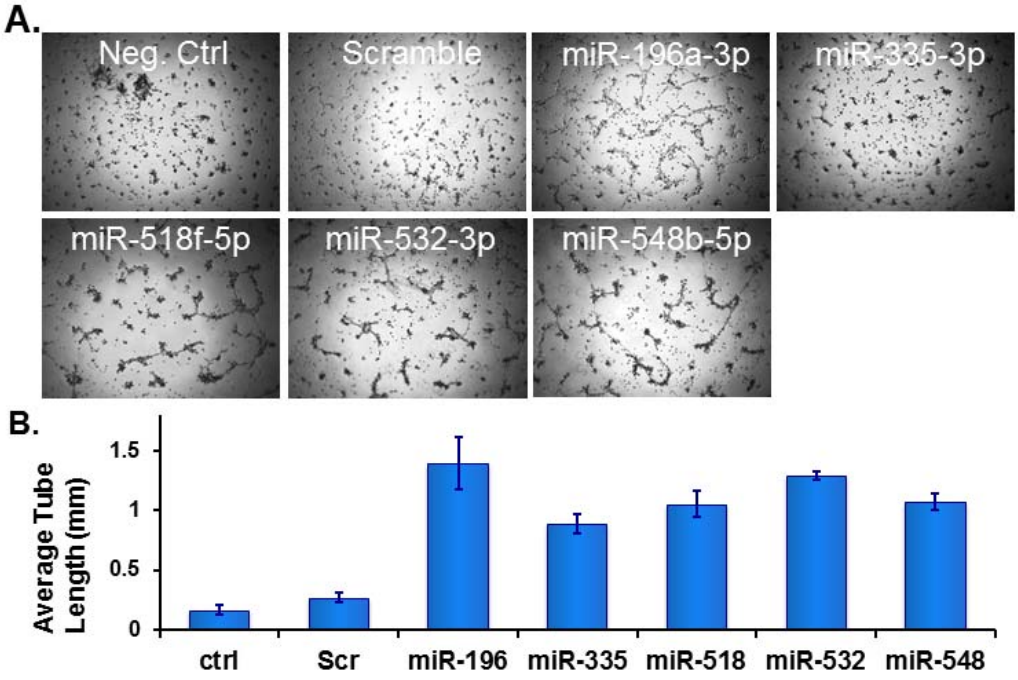
Supplemental IV: Predictive model was created using array data and functional data from Sahoo and Davis laboratories using the complete dataset of miRs.



Supplemental Figure V: Luminex Array of cytokines. Each panel represents levels of the indicated analyte (n=4 in each group). Control = infarct + saline, there was a significant decrease in IL-6, and a significant increase in both IL-1b and IL-18 (anti-inflammatory) with exosome treatment. IL-1a demonstrated a 30% decrease but was not significant (p=0.08). Data are mean ± SEM. *p<0.05 compared with control group (ANOVA followed by Dunnett post-test).



Supplemental Figure VI. Pathway analysis of combined PLSR model from Figure 7. PLSR model identified miRs likely involved in a shared response model of CPCs and CD34-positive cells. Ingenuity pathway analysis was performed to determine pathways targeted by identified miRs. Regulation of cell cycle and cell survival scored the highest.



Supplemental Figure VII. **Pro-angiogenic effects of miRNAs identified from in silico analysis .** HUVECs ($2.5x10^4$) were treated with either miR-196a-3p, miR-335-3p, miR-518f-5p, miR-532-3p, miR-548b-5p or scramble control (30 pmol) overnight followed by plated on Matrigel. Tube length was measured 6 hours later and expressed in mm. **A)** Representative phase contrast images of HUVECs taken by Nikon Microscope with a 2.5x lens. **B)** Comparison of the average of 5 independent wells in total tube length (mm).