EPIGENETIC BET READER INHIBITOR APABETALONE (RVX-208) COUNTERS PROFIBROTIC AND CONTRACTILE ACTIVITY OF CARDIAC FIBROBLASTS WITH POTENTIAL BENEFIT FOR HEART FAILURE

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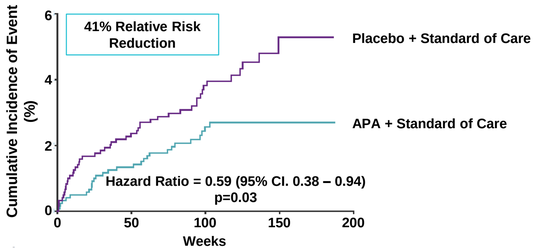
BACKGROUND

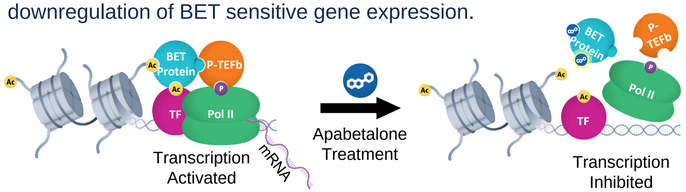
Fibrotic cardiac remodeling contributes to heart failure (HF). Transforming growth factor β_1 (TGF-β_1) initiates profibrotic signaling in the stressed myocardium causing transdifferentiation of cardiac fibroblasts into myofibroblasts that overproduce extracellular matrix (ECM). Inhibition of TGF-β_1 signaling by targeting epigenetic transcription regulators bromodomain and extraterminal domain (BET) proteins is a new therapeutic approach to HF. In the phase 3 BETonMACE trial, patients with type 2 diabetes and a recent acute coronary syndrome receiving the BET inhibitor (BETi) apabetalone had fewer hospitalization for heart failure (HF) than those receiving placebo.



To further understand the BETi mechanism of action in fibrotic heart disease, we examined effects of apabetalone (APA) in TGF-β_1 stimulated human cardiac fibroblasts (CFs).

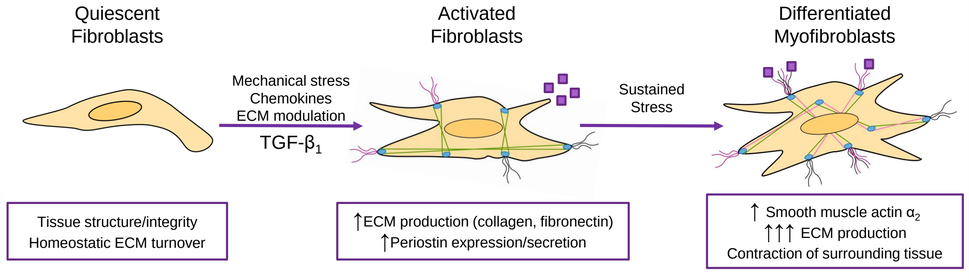
MECHANISM OF ACTION

Apabetalone competitively binds to bromodomains in histone acetylation "readers" termed BET proteins, causing their release from chromatin and downregulation of BET sensitive gene expression.



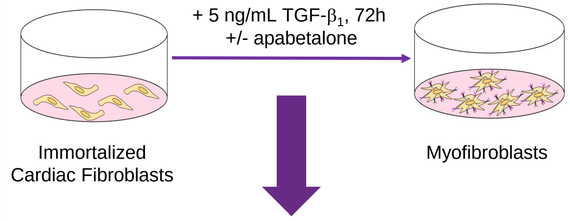
BET: bromodomain and extraterminal proteins; ac: acetylated lysine residue on DNA associated proteins; BD: bromodomain; TF: transcription factor

CARDIAC FIBROSIS PATHWAY



CFs are the main regulators of ECM synthesis and turnover. After myocardial injury, the expression of proinflammatory cytokines and profibrotic factors is upregulated in CFs, leading to increased proliferation and transdifferentiation to myofibroblasts (MFs). MFs alter the ECM composition by secreting elevated levels of collagen and other ECM proteins to maintain the structural integrity of the heart. The excessive and continuous ECM deposition leads to cardiac fibrosis that ultimately causes tissue dysfunction and HF.

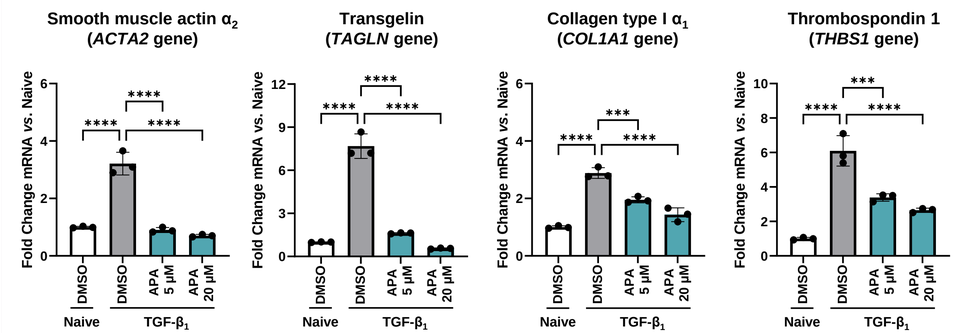
APABETALONE COUNTERS TGF-β_1-INDUCED GENE EXPRESSION BY 50-100%



Gene Expression Analysis:
Cytoskeleton: smooth muscle actin α_2 and transgelin
ECM component: collagen type I α_1
TGF-β_1 activator: thrombospondin 1

Immortalized CFs were treated with TGF-β_1 in the presence of vehicle (DMSO) or apabetalone (APA) in a lysine-coated plastic culture plate. Gene expression of transdifferentiation markers and ECM components were analyzed by real-time PCR. TGF-β_1 stimulation induced the expression of *ACTA2* (3-fold), *TAGLN* (8-fold); *COL1A1* (3-fold); and *THBS1* (6-fold). Cotreatment with 5 µM apabetalone countered TGF-β_1-induced gene expression by 50-100%.

Statistics: 1-way ANOVA with Tukey's multiple comparisons test. ***p<001; ****p<0.0001



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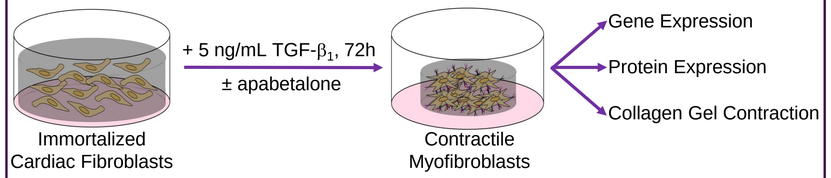
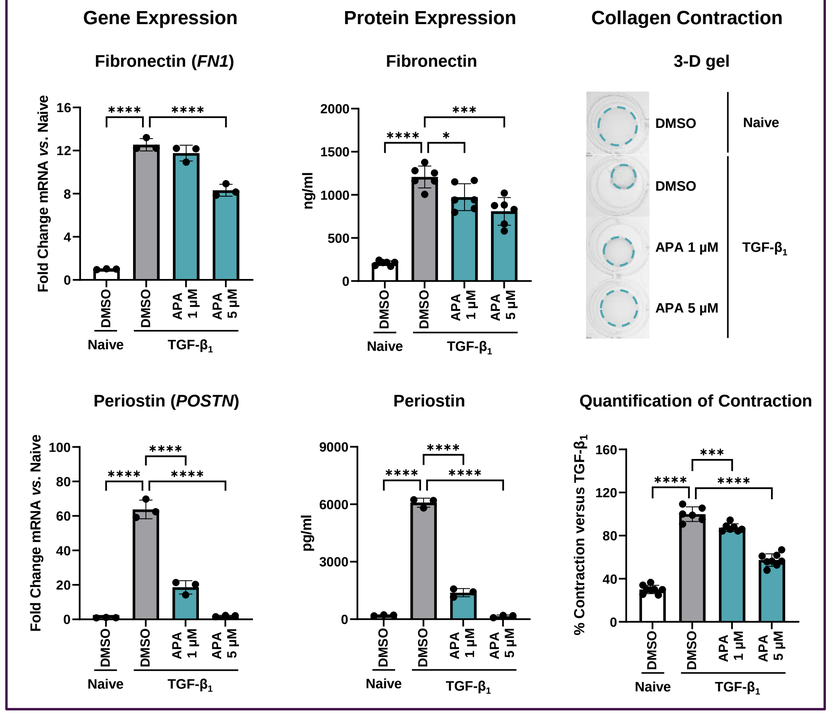
APABETALONE INHIBITS TGF-β_1-INDUCED CONTRACTILE PHENOTYPE



Immortalized CF were cultured with TGF-β_1 in a 3-D collagen gel. After 72h, cells were purified to analyze gene expression, the supernatant was collected to measure protein secretion and collagen gels were imaged to measure the area. Naïve CFs contracted gels by 30% as compared to collagen alone, whereas TGF-β_1 stimulation enhanced gel contraction by 70%. Co-treatment with 1 µM apabetalone reduced gel contraction by 13%, while 5 µM apabetalone reduced gel contraction by 43% when compared to TGF- β_1.

Statistics: 1-way ANOVA with Tukey's multiple comparisons test. *p<0.05; ***p<001; ****p<0.0001



CONCLUSION

1) Treatment with the epigenetic BETi apabetalone reduces transdifferentiation of CFs to MFs and concomitant pro-fibrotic programs, providing mechanistic insight into the observed reduction in hospitalization for HF in apabetalone treated patients with type 2 diabetes and high-risk cardiovascular disease.
2) Apabetalone may provide anti-fibrotic benefits to patients with recent acute coronary syndrome to prevent hospitalization for HF.

DISCLOSURE INFORMATION

SW, ED, LMT,LF, DG, CS, MS, JOJ and EK receive(d) a salary from Resverlogix and own stock and stock options.