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Determination of the mechanisms of ATRA mediated suppression of cardiac hypertrophy

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Pathway analyses of proteomic studies in guinea pig and rat hearts subjected to pressure overload-induced hypertrophy and heart failure (HF) suggest altered retinoid signaling may be a causal contributor to HF progression. This observation is bolstered by our recent studies, where we demonstrated that cardiac levels of all-trans retinoic acid (ATRA) deficient in human patients with non-ischemic HF. This led us to reconsider an old observation that ATRA blocks hypertrophy induced by the a-adrenergic agonist phenylephrine (Phe) in neonatal rat ventricular myocytes (NRVMs). With cross-sectional area (CSA) as an index of hypertrophy, we show, consistent with prior work, that ATRA suppresses Phe-induced increases in NRVM CSA by average of 70%. RT-PCR studies show that ATRA also blunts Phe-induced increases in atrial natriuretic peptide (ANP) gene expression. We then tested the pan-CYP26 inhibitor talarozole (Tala) to raise endogenous ATRA levels, and observed that Tala similarly inhibited Phe-induced increases in NRVM CSA (p<0.001) and ANP expression in a dose dependent manner. ATRA functions biologically through a class of ligand-dependent transcription factors called retinoic acid receptors (RARs) of which there are three isoforms, a, b and ? . To determine through which RARs ATRA and Tala mediate their anti-hypertrophic effects, we used antagonists against each RAR isoform. Initial studies show that the RARb antagonist LE135 (1 µM) fully blocked the action of ATRA (p<0.0001), while initial studies with the RARa and RAR? antagonists (BMS 195614 (1 µM) and MM 11253 (1 µM)) failed to significantly mitigate CSA suppression. This would suggest that RARb is the primary RAR responsible for eliciting the anti-hypertrophic program. However, initial studies with NRVMs virally transduced with siRNA against RARa, b and ? support the more likely conclusion that each RAR may play a role in hypertrophy suppression. Ongoing studies aim to corroborate these findings with Tala mediated hypertrophy suppression. These studies will provide key insights into the mechanisms by which ATRA dysregulation contributes to HF pathogenesis and may aid in the development of more specific therapeutic targets.