**6918: A Steroid Receptor Coactivator Stimulator MCB-613 Attenuates Adverse Remodeling After Myocardial Infarction**

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Previous work from ours and other laboratories have shown that steroid receptor coactivators (SRCs) are involved in heart development and in mitigating cardiac dysfunction in cardiac injury models. Members of the p160 SRC family, SRC-1 (NCOA1), SRC-2 (NCOA2/TIF2/GRIP1) and SRC-3 (NCOA3/AIB1/ACTR/pCIP), interact with nuclear receptors and other transcription factors to drive target gene expression by assembling transcriptional coactivator complexes to increase transcription. This indicates a potential for SRC targeting drugs pertinent to cell migration, proliferation and survival-promoting paracrine interactions in cardiac tissue injury responses. We have identified a small molecule activator of SRCs (MCB-613) that selectively and reversibly binds to SRCs as shown by surface plasmon resonance and is a potent SRC stimulator that acts to greatly enhance SRC transcriptional activity with no apparent toxicity in mice. We postulated that MCB-613 could enable wound repair and preservation of cardiac function after an acute MI by reducing the extent of injury-related fibrosis and the subsequent chronic loss of cardiac function associated with non-contracting scar tissue. We thus tested the effect of MCB-613 on the cardiac injury response by administering MCB-613 two hours after ischemic injury in a mouse model of MI. Along with measurements of functional cardiac output and damage, we sought to identify the cell-type specific responses responsible for MCB-613's cardio-protective effects by utilizing single cell transcriptomics of cardiac interstitial cells to characterize the effects of SRC stimulation on cardiac function post-MI. We show that MCB-613, a potent small molecule stimulator of steroid receptor coactivators (SRCs) attenuates pathological remodeling post-MI. MCB-613 decreases infarct size, apoptosis, hypertrophy, and fibrosis while maintaining significant cardiac function. MCB-613, when given within hours post-MI, induces lasting protection from adverse remodeling concomitant with: (i) inhibition of macrophage inflammatory signaling and IL-1 signaling which attenuates the acute inflammatory response, (ii) attenuation of fibroblast differentiation, and (iii) promotion of Tsc22d3 expressing macrophages - all of which may limit inflammatory damage. Our results indicate MCB-613 controls the cellular interstitial cardiac repair response to ischemia. Distinct molecular and cellular mechanisms related to stimulation of SRC-3 have been identified that pave the way for the further exploration of SRCs as drug targets that can be engaged to improve the management of myocardial injury response outcomes. SRC stimulation with MCB-613 (and derivatives) is a potential novel therapeutic approach for inhibiting cardiac dysfunction after MI.