Genetics Day Poster Submission

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Title: CARDINAL IS A NUCLEAR LNCRNA THAT REPRESSES TCF-SRF-MEDIATED GENE TRANSCRIPTION BY CO-OCCUPYING SRF-BOUND GENE PROMOTERS IN THE HEART

Abstract: LncRNAs are an emerging class of transcriptional coregulators important for balancing cardiomyocyte gene expression networks during heart development, function and disease. We recently characterized a cardiac specific lncRNA, named CARDINAL, which is transcribed upstream of the SRF-coactivator myocardin. Myocardin and members of the ternary complex factor (TCF) family compete for interaction with SRF to promote myocyte contractility vs proliferation. Genetic disruption of CARDINAL in mice resulted in ectopic expression of SRF-TCF target genes, suggesting that CARDINAL functions as an inhibitor of SRF/TCF-mediated gene expression. Here we show using RNA in situ hybridization with RNAScope that CARDINAL transcripts are primarily localized to the nucleus in both mouse and human cardiomyocytes, and did not overlap with other nuclear lncRNAs MALAT1 or NEAT1. Chromatin Isolation by RNA Purification (ChIRP) in HL-1 cardiomyocytes using anti-sense oligonucleotides specific to endogenous murine CARDINAL transcripts, followed by deep sequencing, further revealed that CARDINAL transcripts were localized at ~100 genes in the cardiac genome. The majority of CARDINAL peaks overlapped with ChIP binding peaks for SRF in the heart and were enriched at the transcriptional start sites of SRF-bound gene promoters. Consistent with our previous hypothesis, CARDINAL binding localized mainly to SRF-TCF target genes, including Elk4, Egr1, and components of the AP-1 complex, such as c-Fos, Junb, and Jund. Together, these findings highlight CARDINAL as a novel RNA co-transcriptional regulator of SRF by co-occupying SRF-bound gene promoters.