Submitter Name: Boris Tabakoff
Submitted email: boris.tabakoff@cuanschutz.edu

Are We Going in Circles: Circular RNA as Another Integral Member of the RNA World?

Jennifer Mahaffey[1], Spencer Mahaffey[1], Lauren Vanderlinden[1], Paula Hoffman[1,2], Michal Pravenec[3], Laura Saba[1], and Boris Tabakoff[1];

[1]School of Pharmacy & Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus; [2]Department of Pharmacology, University of Colorado Anschutz Medical Campus; [3]Institute of Physiology The Czech Academy of Sciences, Prague Czech Republic

Non-coding (nc) RNAs are critical control elements of transcriptional and translational events. Circular (circ)RNAs are ncRNAs that are products of back-splicing events which join the 3' and 5' ends of long ncRNA to produce a structure resistant to hydrolysis by exonucleases. One of the most investigated functions of circRNAs is their capacity to sequester (sponge) miRNAs. We investigated the function of circRNAs in heart failure by studying left ventricular hypertrophy (LVH), a precursor to heart failure. We mapped LVH QTLs utilizing a panel of RI rats (HxB·BxH), which are a subset of the HRDP rat panel known to demonstrate quantitative differences in cardiovascular traits. We measured 122 circRNAs differentially (FDR<0.05) expressed in the left ventricle between the parental strains of the RI panel (BN and SHR), but only one was located in the area of the genome defined by a QTL for LVH. If a QTL defines an area of the genome contributing to a phenotype, then an element coded in this region should impact the phenotype. The circRNA we identified (circH2afy) has multiple sites for binding mir-210-5p which in turn, has a binding site on the 3' UTR of *Tnfrsf21* and controls its translation. Tnfrsf protein (aka: Death Receptor 6) activates NFkB, which is required for a hypertrophic response in the heart. Our studies demonstrate the power of using the components of the HRDP for trait mapping studies and deep quantitative analysis of total RNA for insights into the drivers of complex traits.

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