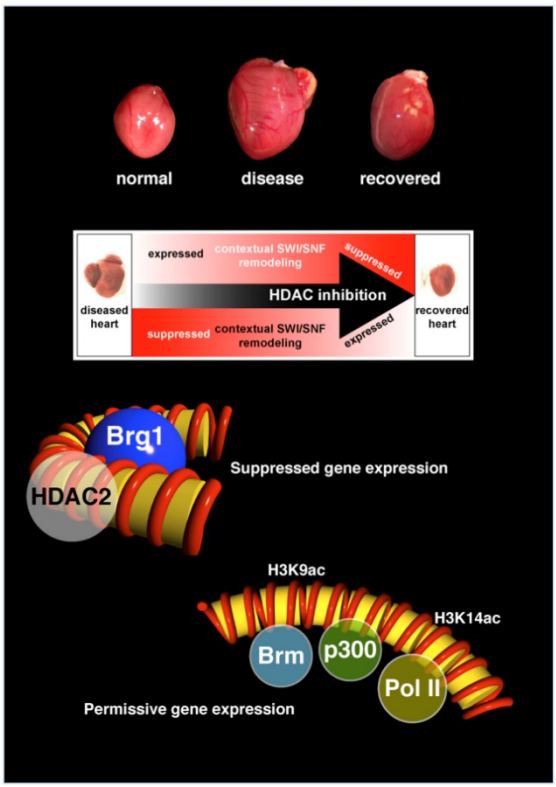
ncRNAs and histone code changes mediate epigenetic events and gene expression in heart disease

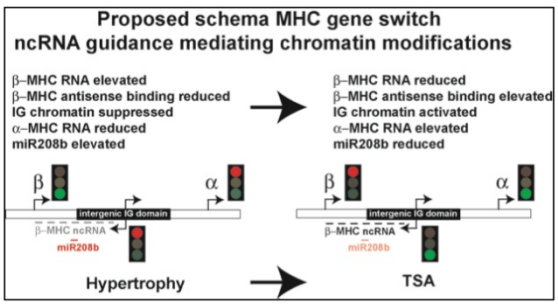
Overview

Heart disease remains the leading cause of death in many developing countries. Myocardial hypertrophy is an initiatory hallmark of cardiac failure, which is now recognized as a response to genetic, physiologic and environmental changes. Despite the advances in the field of heart disease and regenerative medicine as well as the identification of signaling pathways that distinguish molecular events associated with heart failure, a fundamental question remains; what is the environmental consequence or the role of epigenetic changes on the cardiovascular system? Emerging evidence indicates that important epigenetic changes, more specifically, changes in histone modifications appear to be associated with the induction of gene regulatory events in the hypertrophied heart.

Histone deacetylase (HDAC) activity is thought to play an important role in cardiac development and recent reports have indicated opposing roles in hypertrophy. This now represents a central paradigm in heart development and disease. The chromatin remodeling enzyme-Brg1 was identified to contribute to heart muscle development and was associated with the MHC transcriptional switch.



The hypertrophic myocardium is characterized by profound changes in gene expression. Although the precise nature of fetal gene regulation remains poorly defined, we know that transcription of ANP, BNP, β-MHC and Acta1, are reactivated in the hypertrophied heart is associated with inactivation of α-MHC, SERCA2a, b1-AR genes, which is the basis for altered morphology and function in hypertrophic myocardium. These genes are associated with changes in a range of cardiac conditions with strong evidence that altered MHC genes impacting on hypertrophic growth with a decline in contractile function.



There is also emerging evidence that non-coding RNA (ncRNA) sequences can drive gene changes and specifically direct transcriptional regulation. This area of research has previously been performed in a non-integrated manner, and therefore precisely how these mechanisms collectively operate in the diseased heart remains poorly understood. We have experimental evidence that ncRNAs and histone code changes mediate chromatin-remodeling events that confer gene expression changes in cardiac hypertrophy. We believe chromatin remodeling enzymes can be considered important in the maintenance of gene

silencing and activation events in the heart. This represents a new model of gene regulation in cardiac hypertrophy with context-dependent reprogramming directed by ncRNAs.

Hypothesis and Project Aims

In this project we propose that ncRNA can acts as a substrate for epigenetic changes that are associated with coding RNA expression. The specific aims of the project include;

- Determining the role of chromatin modifications in the context of ncRNAs and understanding the opposing roles of remodeling enzymes in the control of gene programs for pathological cardiac hypertrophy

- Exploring RNA directed gene regulation and the reversal of cardiac hypertrophy using HDAC inhibitors

Overall Project Outcomes and Significance

This project is designed to address a key issue regarding how pathological stimuli are finally converted into an altered gene expression profile that eventually leads to cardiac hypertrophy and heart failure. While it has been known for years that epigenetic pathways, specifically, chromatin remodeling functions as a terminal step in modulating gene transcription, its role in influencing gene expression with aging, hypertrophy and heart failure remain poorly characterized.