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Dawn of The Epi-LncRNAs: New Path from Myheart

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Abstract

Myheart is a cardiac specific long-noncoding (lnc) RNA with targeted modulation of chromatin modifying SWI/SNF complex via direct interaction with Brg1. Genetic induction of Myheart in mouse heart has a significant protective effect against the pathogenesis of heart failure. LncRNAs are emerging epigenetic regulators with potentially important roles in cardiac development and diseases.

Recent advances in genomics studies have revealed a profound new insight: the vast majority of our genome is no longer viewed as gene "wasteland" but actually littered with previously unrecognized harbors where many species of non-coding transcripts are produced¹. Among the different species of non-coding transcripts, long non-coding (lnc) RNAs, arbitrarily defined as transcripts longer than 200 nt with no or little translation propensity, represent a relatively new and understudied class. To date, majority of the nuclear lncRNAs are identified as histone modifiers that can epigenetically regulate transcriptome¹. These lncRNAs, which we refer here as Epi-lncRNAs, define a new paradigm of epigenetic regulation implicated in development and human diseases. In a recent report in *Nature*, Han et. al, identify the myosin heavy-chain-associated RNA transcripts (Myheart, or Mhrt) as an important regulator of cardiac hypertrophy and pathological remodeling through direct interaction with Brg1, the ATPase catalytic subunit of the switching defective/sucrose non-fermenting (SWI/SNF) complex²³. This finding brings new spotlight to Epi-lncRNAs in cardiac gene regulation and pathogenesis, and reveals Brg1 as a new lncRNA-regulated histone modifier (Figure 1).

The onset and progression of heart failure is associated with and driven by a concerted global change in cardiac gene expression, including re-expression of a subset of fetal genes^{4, 5}. A well studied example is the dynamic switch between the α - and the β -myosin heavy chain (MHC) isoforms during postnatal cardiac maturation and pathology. This switch is carried out by coordinated and reciprocal up- and down-regulation of Myh6 (gene for α MHC) and Myh7 (gene for β MHC) which are clustered in tandem on a highly conserved genomic locus. Previous work from Chang lab has demonstrated that epigenetic regulation through Brg1 is critical to both induction of Myh6 and repression of Myh7 involving direct interaction with histone deacetylase (HDAC) and Poly (ADP-ribose)

polymerase 1 (PARP1) ⁶. Although chromatin remodeling has long been recognized as an important mechanism in cardiac transcriptome programming and reprogramming during development and pathogenesis, it remains a mystery as to how ubiquitously expressed chromatin remodeling complexes such as SWI/SNF can confer tissue-specific and coordinated regulation on their cardiac target genes. The discovery of Mhrt provides an intriguing mechanism for the underlying molecular process. Mouse Mhrt expression is induced during cardiomyocyte maturation and reduced in pressure overload-induced cardiac hypertrophy and heart failure, a profile perfectly correlated with the dynamic changes in the Myh7/Myh6 ratio during postnatal development and disease progression in heart. Transgenic mice expressing Mhrt show a blunted change in Myh7/Myh6 ratio in response to pressure overload. Mechanistically, by using procedures like RNA co-immunoprecipitation and EMSA, Han et al. provide a series of evidence that Mhrt directly binds to the helicase domain of Brg1 which inhibits Brg1 chromatin-interacting capability, leading to selective repression of Myh6 and Mhrt expression in failing hearts. Thus, authors conclude that Mhrt regulates cardiac hypertrophic gene reprogramming via direct modulation of Brg1 mediated chromatin remodeling.

Mhrt transcripts are detected with a transcriptional start site overlapping but in the opposite direction with the Myh6 promoter and the transcripts are extended into the Myh7 intron and exon sequences³. Thus, Mhrt possesses both features of a promoter-associated lncRNA and an anti-sense lncRNA regarding Myh6 and Myh7 respectively. However, anti-sense effect unlikely plays a major role in Mhrt mediated regulation considering the observations that Mhrt effect is dependent on Brg1 and that over-expressing Mhrt alone has no significant effect on Myh6/7 expression in cultured myocytes or transgenic hearts under basal condition. Furthermore, gene expression profiling and targeted chromatin-immunoprecipitation (ChIP) analysis have also revealed that the impact of Brg1/Mhrt interaction goes beyond *cis*-regulation at the Myh6/7 locus but affects *in-trans* other cardiac genes. Such broad impact explains why Mhrt expression *in vivo* can have such significant impact on the whole spectrum of pathological features in stressed heart. Indeed, Brg1 also acts on the Mhrt promoter itself forming a negative circuit regulation, implicating that the chromatin remodeling may be critical for establishing a stable expression level of target genes.

In addition to Mhrt, a number of other epigenetic mechanisms have been reported to control Myh7 and Myh6 expression during heart diseases. miR-208a and miR-208b, embedded in the introns of Myh6 and Myh7 genes respectively, regulate Myh7 expression via downstream targets Thrap1 and Myostatin ^{7, 8}. A recent study identified another lncRNA cardiac hypertrophy related factor (CHRF) that regulates Myh7 expression by acting as a sponge for miR-489². The fact that different and diverse regulatory circuits converge at Myh6 and Myh7 gene cluster illustrate the importance of fine-tuning Myh7/Myh6 expression for normal cardiac function and the progression to disease under stress (Figure 1). In this regard, Myh6 and Myh7 are not simply sarcomere genes for the infrastructure of cardiac contraction⁹, but also a central command for global cardiac gene regulation in development and diseases.

Despite of these exciting new findings, for the vast majority of known cardiac lncRNAs, their biological functions remain elusive. Even in the case of Mhrt, the investigation opens many more questions than answers. Brg1 has been shown to interact with multiple transcription regulators in addition to HDAC/PARP¹⁰ and the impact of Mhrt interaction on their function remains to be studied. Finally, critical insights are still missing as to why the impact of Mhrt/Brg1 complex leads to opposite effects on Myh6 versus Myh7 expressions. Also demonstrated in both reports are the current challenges in lncRNA investigations. Simple sequence analysis is not sufficient to assure the non-coding feature of the putative lncRNAs and rigorous experimental validation by ribosome profiling, in vitro translation and targeted mutagenesis are required. In the absence of sequence constraints to lncRNA function, there is an urgent need to better understand the structural basis of lncRNA function. Poor sequence conservation also raised questions about clinical relevance and translation of lncRNA studies in animal models. Nevertheless, current progress has demonstrated great promise for lncRNAs as novel and potentially powerful biomarkers for disease diagnosis, prognosis and stratification¹¹¹²¹³. The intricate regulatory circuits of lncRNA as demonstrated by CHRF and Mhrt provide potential new targets for therapeutic intervention. Considering the fact that vast majority of the genetic variants reside in the non-coding part of the human genome, better understanding lncRNA biology would offer new insights to the molecular basis of genetic diversity and personalized medicine for human diseases including heart failure. Clearly, more investigations both at molecular level and systems level are required to advance our current knowledge to these new players in cardiac regulatory circuits.

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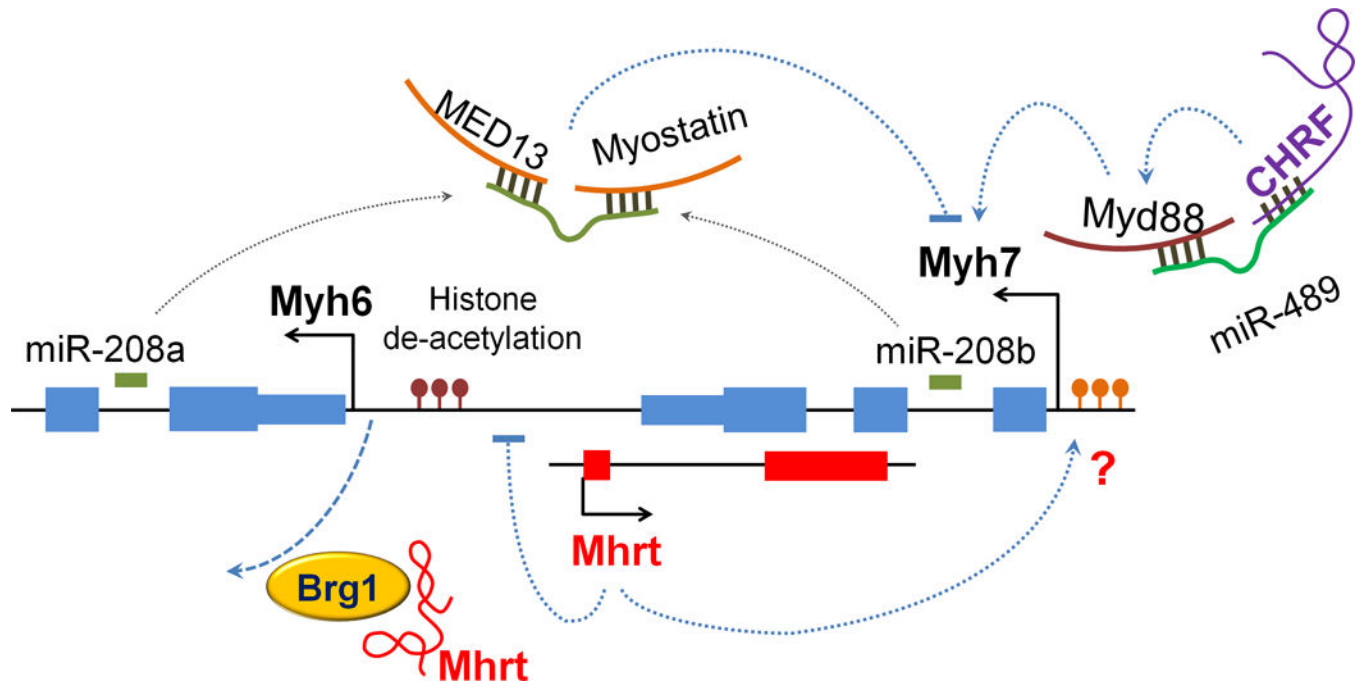


Figure 1. Epigenetic regulations by long non-coding RNAs (lncRNAs)
Regulatory circuit of α - and β -myosin heavy chain (*Myh6* and *Myh7*) involving diverse epigenetic regulators.