

Modern of progenitor and embryonic stem cells

[Technology](#), [Development](#)



Modern transcriptomics profiling and loss-of-function (LOF) methodologies of progenitor and embryonic stem cells (ESCs) avails the importance of lncRNAs for cardiac development and cell differentiation. More than 1, 000 lncRNAs were found to be dynamically regulated during differentiation 110, 111, which identifies lncRNAs specific to tissue and developmental stage by analysis of adult and embryonic hearts 112, 113. Among the functionally analysed lncRNA some of them are involved in cardiac developments.

Braveheart (Bvht) is a long non-coding transcript specifically expressed in embryonic stem cells, which is required for differentiation into cardiac cells 104. Bvht regulates a core cardiac transcriptional network by targeting PRC2 to cardiac lineage-specific gene promoters.

Additionally, Bvht is required for the maintenance of cardiac fate in primary cell cultures of cardiac fibroblasts 104. Fendrr (fetal-lethal non-coding developmental regulatory RNA) is a lncRNA expressed in the lateral plate mesoderm during embryonic development and in high levels in the mesoderm derivatives of the adult lung 105. Inactivation of Fendrr through the insertion of a premature Poly-A signal leads to embryonic lethality at E13. 75 due to heart and body wall defects 105.

Interestingly, a second knockout mouse was generated that entirely deletes the Fendrr gene; this mouse exhibited perinatal lethality likely due to a vascularization defect in the lungs. Fendrr has the ability to bind both PRC2 and TrxG/MLL protein complexes and affect chromatin modifications at lineage-specific loci 105. Recently, enhancer-associated lncRNA Novlnc6 showed to regulate the expression of cardiac transcription factor NKX2-5 that is important for cardiac differentiation and maturation 114. Another lncRNA, <https://assignbuster.com/modern-of-progenitor-and-embryonic-stem-cells/>

CARMEN (cardiac mesoderm enhancer-associated non-coding RNA) was also showed to interact with PRC2 and to be involved in cardiogenic specification and differentiation in precursor cells, possibly by regulating PRC2

114. Recent studies have publicized the association of lncRNAs in cardiac diseases 115-125.

Interestingly, dysregulation of certain lncRNAs causes a similar phenotype in both human and rodent models (Figure 5) 115. Some studies showed the role of lncRNAs in hypertension, coronary artery disease (CAD), MI, ischemia, and heart failure. SENCR and H19, for example, are widely implicated in cardiovascular disease. SENCR reported to be downregulated in vascular smooth muscle cells (VSMCs) from a type 2 diabetes mellitus murine model, promoting proliferation and migration 116. Another antisense non-coding RNA H19 showed to inhibit cell proliferation and regulates embryonic development 117.

Moreover, human genome-wide association studies (GWASs) have demonstrated significant associations between H19 locus and systolic or mean arterial blood pressure, linked to hyperhomocysteinemia, a known risk factor for CAD 118, 119. Of note, H19 sponge let-7 family miRNAs 90, 120, which are speculated as atheroprotective 121-124 or proatherosclerotic roles and are downregulated in CAD patients 125. MIAT lncRNA was found to increase the cardiac hypertrophy, a pathological condition occurring after myocardial infarction. A SNP reported in MIAT locus facilitates its transcription and regulates binding to its protein partners and its function as sponge for miR-150 128. Similarly, LIPCAR, a circulating lncRNA identified in

plasma of acute myocardial infarction patients, showed to be dysregulated in different stages of AMI. Specifically, it was downregulated early after AMI, but was higher expressed in later stages 129. The well-known lncRNA MALAT1 which expression is increased by hypoxia in endothelial cells in vitro and also upon hind limb ischemia in vivo. MALAT1 is described to be important for the formation of vessel-like structures and depletion increases migration of tip-cells but impedes proliferation of stalk cells 131.

Recent studies highlighted that the lncRNA Chast (cardiac hypertrophy-associated transcript) influences cardiomyocyte hypertrophy. In vivo studies showed that Chast is specifically upregulated in cardiomyocytes in transverse aortic constriction (TAC) operated mice 146. Likewise, lncRNA-ROR interacts with miR-133 influences cardiac hypertrophy by elevated expression of fetal genes, i. e.

atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) respectively 147. More recently, a report showed lncRNA MANTIS has a role in angiogenic sprouting and endothelial cell function. MANTIS regulates transcription of key endothelial genes and stabilizes the ATPase activity of BRG1 by direct interaction 132. LncRNAs potentially represent a powerful tool for personalized medicine due to their specific expression patterns associated with distinct pathologies.

There are numerous hurdles to develop specific therapeutic intervention including the heterogeneity of expression, specific delivery of the ASOs or pharmacological agents, as well as their penetration into the intracellular compartment of interest. Taken together, lncRNAs possess enormous

potential therapeutics, which much remains to be fully unveiled. In order to implement this, fine molecular mechanism of disease pathogenesis and gene regulation has to be finely elucidated.