Long Non-Coding RNAs in Cardiovascular Diseases

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Cardiovascular diseases (CVDs) are the leading cause of death worldwide. It is estimated that approximately 18.5 million people die annually on account of these diseases, with a third of these people dying under the age of 70 years. Identifying those most affected by CVDs and ensuring they receive the appropriate treatment can prevent premature deaths. Furthermore, the development of new therapeutic strategies and biomarkers with the potential to predict the progression of CVDs is fundamental to reducing mortality worldwide. CVDs can be defined as disorders that affect the heart or blood vessels such as heart failure, coronary heart disease, cerebrovascular disease, peripheral arterial disease, and congenital heart disease.

Keywords: aerobic training ; lncRNAs ; cardiovascular disease ; biomarkers

1. Introduction

The main risk factors associated with these diseases are smoking, excessive alcohol consumption, sedentary lifestyle, obesity, high blood cholesterol, among others. Individuals at risk of developing CVDs may, therefore, have increased blood pressure, glucose, and triglycerides as well as overweight and obesity. Among the many risk factors that predispose to the development and progression of CVDs, a sedentary lifestyle, supported by consistently low levels of physical activity, represents a major contributor to CVDs. On the other hand, regular exercise is associated with health benefits and a lower risk of disease [1][2]. Several studies have demonstrated that increased physical activity promotes a reduction in all-cause mortality and can increase life expectancy, affecting a strongly link to a decline in the risk of developing CVDs, in part by promoting weight loss, blood pressure control as well as improving blood lipid profile and insulin sensitivity [1][3]. For these reasons, physical activity has been recommended worldwide for CVD prevention and treatment. Despite the benefits of regular physical exercise, the molecular mechanisms by which they occur are still poorly understood.

In recent decades, a research effort has been aimed at identifying the major physiological, biochemical, and molecular contributors to the cardiovascular benefits of exercise. This research resulted in advances obtained from observational studies and interventions in both human and animal models. The Encyclopedia of DNA Elements (ENCODE) [4], a project realized in 2012, challenged the central dogma of biology and the interpretation of what is considered a functional region of the human genome [5]. From the use of high-throughput genomic platforms, it was discovered that the coding transcripts (i.e., mRNAs) represent less than 3% of the genome, while everything else represents transcripts that have little or no ability to synthesize protein. These transcripts are called non-coding RNAs (ncRNAs) [6]. For a long time, these non-coding transcripts were neglected and treated as “junk of the DNA” [7][8], “transcription noise” [9][10][11], or even as “dark matter of the genome” [12][13]; however, evidence shows that ncRNAs are not only functionally active as RNA molecules but are also one of the major regulatory networks of gene expression at the epigenetic, transcriptional, and even post-transcriptional levels (for more information, see References [8][14][15][16][17]).

According to the number of nucleotides (nt), ncRNAs can be divided into two large classes: those with fewer than 200 nt, called small non-coding RNAs such as microRNAs (miRNAs), and those with more than 200 nt, called long non-coding RNAs (lncRNAs). Among them, miRNAs are better understood and act mainly in post-transcriptional control as protein synthetic silencers binding to their target mRNA on which they induce translation degradation or repression [18]. The identification of stable miRNAs in body fluids, a strong indicator of cell-cell communication via circulating RNAs, suggested for the first time the possibility of non-coding transcripts serving as diagnostic and prognostic biomarkers for several diseases [19][20] as well as the possibility of their being used as therapeutic targets and monitoring of physical performance induced by exercise training [21][22][23][24]. On the other hand, lncRNAs can modulate gene expression at multiple levels and in an even more complex way than a regulation made by miRNAs [25][26][27]. However, lncRNAs have only recently attracted the attention of researchers, and knowledge about them, including their potential as a biomarker and therapeutic target, is still limited [28][29][30][31].

According to the LncRNA Disease v2.0 database (www.rnanut.net/lncrnadisease, accessed on 16 September 2021), there are currently more than 205,959 associations between lncRNAs and diseases including CVDs. As knowledge about these associations grows, so does the interest in investigating the influence of exercise training on the modulation of the expression of these transcripts and the possibility of using the health benefits as potential therapeutic targets [32][33][34].

2. LncRNAs in Cardiovascular Diseases

lncRNAs can be correlated with many human diseases [35][36][37][38] including CVDs. The first association between lncRNA and heart disease came from genetic studies in which it was discovered that the locus enriched in single nucleotide polymorphisms involved with myocardial infarction susceptibility was not actually a protein-coding locus but coding for an ncRNA, which the discoverers named MIAT (myocardial infarction-associated transcript) [39]. Since then, several studies have reported associations between lncRNAs and CVDs (**Table 1**).

Table 1. List of lncRNAs involved in cardiovascular diseases.

lncRNA	CVDs	Association	References
aHIF	MI	Regulation of the angiogenesis process and a biomarker.	[40]
aHIF	CHD	Biomarker.	[41]
AK098656	AH	Regulation of arteries of resistance and a biomarker.	[42]
ANRIL	CHD	Susceptibility conferred by SNPs in the ANRIL locus on chromosome 9p	[43]
ANRIL	AH	Increase of susceptibility to higher systolic blood pressure conferred by polymorphisms.	[44]
ANRIL	MI	Protection of cardiomyocytes from hypoxia by acting on the miRNA-7-5p/SIRT1 axis; and biomarker to LV dysfunction.	[45][46][47]
ANRIL	HF	Biomarker.	[48]
APF	MI	Promotion of cardiomyocytes autophagy acting as a sponge for miRNA-188-3p.	[49]
APOA1-AS	CHD	Biomarker.	[41]
AWPPH	CHD	Biomarker.	[50]
BACE1-AS	HF	Promotion of ECs apoptosis.	[51]
BANCR	CHD	Promotion of VSMCs proliferation and migration.	[52]
CARL	MI	Reduction of mitochondrial fission and apoptosis acting as a sponge for miRNA-539.	[53]
CDR1AS	MI	Biomarker.	[54]
Chaer	HF	Induction of Pathological cardiac remodeling.	[55]
Chast	HF	Induction of Pathological cardiac remodeling.	[56]
CHRF	HF	Endogenous sponge to miRNA-489 activity.	[57]
CHROME	CHD	Regulation of cellular cholesterol homeostasis.	[58]
CoroMarker	CHD	Biomarker.	[59]
EGOT	HF	Biomarker.	[48]
FTX	MI	Regulation of cardiomyocytes apoptosis acting as a sponge for miRNA-29b-1-5.	[60]
GAS5	AH	Regulation of ECs and VSMCs function acting as endogenous RNA competing of miRNA-21; and a biomarker.	[61][62]
GAS5	MI	Protection of cardiomyocytes against hypoxic injury acting as a sponge for miRNA-142; promotion of the development and progression of the disease acting on the miRNA-525/CALM2 axis; and improves apoptosis by negatively regulating sema3a.	[63][64][65]
Giver	AH	Promotion of VSMCs dysfunction.	[66]
H19	MI	Induction of cardiac remodeling; autophagy; and biomarker.	[67][68][69]

lncRNA	CVDs	Association	References
H19	CHD	Biomarker.	[70][71]
H19	HF	Regulation of cardiac hypertrophy; and a biomarker.	[48][72]
HEAT2	HF	Biomarker.	[73]
HOTAIR	MI	Induction of cardioprotective acting as a sponge for miRNA-1 and as a biomarker.	[74]
HOTAIR	HF	Biomarker.	[48]
HOTTIP	CHD	Promotes ECs proliferation and migration.	[75]
HRCR	HF	Inhibition of cardiac hypertrophy acting as a sponge for miRNA-223.	[76]
KCNQ1OT1	MI	Biomarker for left ventricular dysfunction.	[45]
LIPCAR	MI	Biomarker for cardiac remodeling.	[77]
LIPCAR	CHD	Biomarker.	[78]
LIPCAR	HF	Biomarker.	[77]
lincRNA-p21	CHD	Regulation of cardiomyocytes apoptosis and proliferation.	[79][80]
LINC00968	CHD	Promotion of ECs proliferation and migration acting as a sponge for miRNA-9.	[81]
lincRNA-ROR	HF	Regulation of cardiac hypertrophy acting as a sponge for miRNA-133.	[82]
Lnc-Ang362	AH	Regulation of VSMCs proliferation through miRNA-221 and -222.	[83]
Lnc-Ang362	MI	Promotion of cardiac fibrosis.	[84]
LOC285194	HF	Biomarker.	[48]
MALAT1	MI	Regulation of cardiomyocytes apoptosis and autophagy through miRNA-558; and biomarker.	[69][85][86]
MALAT1	CHD	Biomarker.	[87]
MDRL	MI	Reduction of mitochondrial fission and apoptosis acting as a sponge for miRNA-361.	[88]
MEG3	MI	Regulation of cardiomyocytes apoptosis.	[89]
MEG3	HF	Regulation of cardiac fibrosis and diastolic dysfunction.	[90]
MHRT	MI	Regulation of cardiomyocytes apoptosis; and biomarker.	[91]
MHRT	HF	Regulation of chromatin remodelers; and biomarker.	[92][93]
MIAT	MI	Regulation of cardiac hypertrophy and fibrosis acting as a sponge for miRNA-150 and -93.	[39][94][95]
MIAT	CHD	Biomarker.	[87]
MIAT	HF	Regulation of cardiac hypertrophy acting as a sponge for miRNA-150.	[95]
Mirt1/2	MI	Regulation of cardiac remodeling.	[96]
n379519	MI	Promotion of cardiac fibrosis through miRNA-30.	[97]
NEXN-AS1	CHD	Mitigation of atherosclerosis.	[98]
NONRATT021972	MI	Promotion of cardiac function.	[99]
NR_027032	AH	Biomarker.	[100]
NR_034083	AH	Biomarker.	[100]
NR_104181	AH	Biomarker.	[100]
NRF	MI	Regulation of cardiomyocytes necrosis.	[101]
NRON	HF	Biomarker.	[93]
PCFL	MI	Promotion of cardiac fibrosis through miRNA-378.	[102]
RMRP	HF	Biomarker.	[48]

lncRNA	CVDs	Association	References
RNY5	HF	Biomarker.	[48]
SMILR	CHD	Biomarker.	[103]
SOX2-OT	HF	Biomarker.	[48]
SRA1	HF	Biomarker.	[48]
TTTY15	MI	Induction of cardiomyocyte injury by hypoxia targeting miRNA-455.	[104]
UCA1	MI	Biomarker.	[105][106]
UIHTC	MI	Promotion of mitochondrial function.	[107]
Wisper	MI	Regulation of cardiac fibroblast.	[108]
ZFAS1	MI	Induction of cardiomyocyte apoptosis; cardiac contractility reduction; and biomarker.	[54][107][109]

AH, arterial hypertension; CVDs, cardiovascular diseases; CHD, coronary heart disease; ECs, endothelial cells; HF, heart failure; lncRNA, long non-coding RNA; MI, myocardial infarction; miRNA, microRNA; VSMCs, vascular smooth muscle cells; SNPs, single-nucleotide polymorphisms.

Given the specificity of expression of lncRNAs, it would be careless to think that the dysregulation of the expression of these molecules in cardiac pathological processes, even if the molecular mechanism behind them is not exactly understood, was a mere coincidence [110]. The poor conservation of these interspecies transcripts, however, makes it difficult to translate findings in rodent models for human applications; however, several studies have shown promising results regarding the prognosis of CVDs and new therapies from the modulation of cardiac lncRNAs [32][33][111][112][113][114][115]. We summarize the lncRNAs and the CVDs (**Figure 1**).

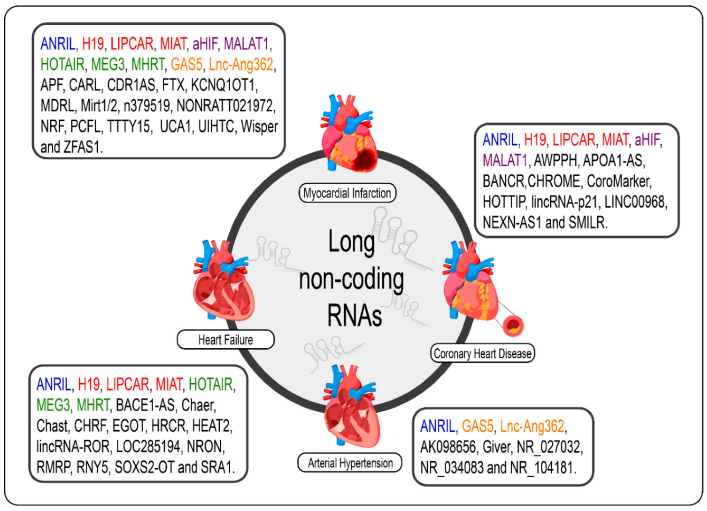

Figure 1. lncRNAs are differentially expressed in cardiovascular diseases such as heart failure, myocardial infarction, coronary artery disease, and arterial hypertension. The lncRNAs marked in blue are the same present in myocardial infarction, coronary artery disease, heart failure, and arterial hypertension; those marked in red are the same present in myocardial infarction, coronary artery disease, and heart failure; those marked in green are the same present in myocardial infarction and heart failure, those marked in orange are present in myocardial infarction and arterial hypertension; and the purple present in myocardial infarction and coronary artery disease.

3. LncRNAs in Cardiovascular Diseases: Challenges and Future Perspectives

lncRNAs have characteristics of great interest to the biomedical community. These characteristics have received attention, albeit timidly, in recent clinical trials (NCT04189029; NCT03268135; NCT02915315; NCT03279770) to investigate the role of these transcripts as biomarkers and in the pathogenesis of some CVDs. However, one cannot fail to mention the challenges to be overcome until these transcripts finally move from research to clinical application.

The isolation, detectability, quantification, and strategy adopted for the normalization of circulating lncRNAs are key factors for the reliable identification of candidates as potential biomarkers and, in the absence of standardization, have

been technical limitations of important relevance for ncRNAs in general [116][117][118]. Added to this is the fact that there may be significant variations in the expression levels of lncRNAs, including those that are significant regarding CVDs, among different body fluids such as serum, plasma, and urine or even among different compartments of the same cell [119][120]. The lack of standardization regarding the fluid to be considered as a sample for a given lncRNA may end up leading to research with wrong conclusions. In addition, cardiovascular risk factors, medication use, sex, and age are examples of some factors capable of promoting changes in the expression levels of ncRNAs such as lncRNAs [121][116]. Among the limitations found in the process until lncRNAs reach the clinic stage as therapeutic targets is the fact that lncRNAs are still in the process of characterization and annotation; even at these stages, many challenges need to be overcome. In this sense, the modulation of a lncRNA can result in opposite effects, even harmful, for the purpose in question [33], since the same lncRNA can be involved in the mechanism of different pathologies [122][123]. The availability of information on the characterization and annotation of lncRNAs, therefore, provides greater knowledge about the lncRNA in question and, consequently, of other molecules with which it may be related, which allows a broader notion about the implications involved in the modulation of one of these transcripts. Furthermore, it is well known that the intermediate step between basic research and clinical trials necessarily involves the use of animal models. At this point, the lack of conservation of the nucleotide sequence of lncRNAs among different species represents a limitation with great impact, as it makes it difficult to transpose the results obtained in preclinical studies to humans [124]. Therefore, clinical trials end up being restricted to working only with those lncRNAs that have their counterparts in humans. In addition to these challenges, there is still a need to elucidate the secondary and tertiary structures of lncRNAs, which are even more critical for the function of these transcripts than the primary structure, and these may have structural homologues in other species including those used as models of experimental animals [125][126]. Finally, there are still challenges regarding drug delivery to the target lncRNA of interest [127].

Considering the limitations mentioned here, an initiative by the scientific community is needed to reach a consensus on the methods (from the way the sample is manipulated to the chosen normalization strategy) to be used to ensure robust paths for identifying lncRNAs as CVD biomarkers as well as precision regarding the criteria and parameters to be adopted for the formation of groups involved in future clinical studies, whether for the identification of lncRNAs as biomarkers or the assessment of their potential as a therapeutic target. In this regard, there is still much to be overcome regarding the challenges of the application of lncRNAs as a therapeutic approach in CVDs; the clinical trials presented here refer mostly to the use of these molecules as biomarkers, some of which also investigated the role of lncRNAs in CVDs. Although important experiments using highly sophisticated technological tools, such as RNA-seq, have been conducted to identify therapeutic candidate lncRNAs, little has been done regarding the characterization of these transcripts found in terms of regulation of the pathological process or ability to undergo regulation. It is necessary, therefore, that new information that arises about a lncRNA already known or recently discovered can be accessed by any researcher, anywhere in the world, as this ensures optimization in the field of research on lncRNAs. Even today, the lack of gene homology is an obstacle in science. Future technological advances are expected to provide solutions to overcome these and other limitations that challenge the use of lncRNAs as therapeutic targets in CVDs [33][116][117][127]. Once overcome, the benefits for patients affected by CVDs can be enormous.

4. Conclusions

This new class of non-coding transcripts playing regulatory roles in various diseases is the beginning of knowledge. Although the number of lncRNAs discovered over the years has increased, so far very little is known about the mechanisms of action and functions performed by these molecules. One of the reasons for this delay is the poor sequence conservation of interspecies lncRNAs, as variations in different animal models make the identification of biological functions and mechanisms of action of the vast majority of lncRNAs and the consequent translation of findings from animals to humans difficult. In this aspect, databases (for example, LNCipedia [128], LncTar [129], and LncRNAWiki [130][131]) have been important tools for depositing and rationalizing information about lncRNAs from different parts of the world. Despite the challenges, lncRNAs are promising candidates for therapeutic use and are characterized as a tool with great application power in personalized medicine given their specific expression pattern associated with different pathologies. It is still the beginning of this new field of study involving the modulation of the expression of lncRNAs in the context of CVDs and physical exercise. There are, therefore, great expectations regarding the application of alternative modalities to aerobic exercise to modulate the lncRNAs involved in this context, such as resistance training and also combined training. Before therapeutic application, further research is needed for a complete functional characterization of lncRNAs involved in cardiovascular pathology as well as their ability to be regulated from different physical training protocols.

References

1. Sharma, S.; Merghani, A.; Mont, L. Exercise and the Heart: The Good, the Bad, and the Ugly. Eur. Hear. J. 2015, 36, 1445–1453.
2. Pedersen, B.K.; Saltin, B. Exercise as Medicine-Evidence for Prescribing Exercise as Therapy in 26 Different Chronic Diseases. Scand. J. Med. Sci. Sports 2015, 25, 1–72.
3. Dunstan, D.W.; Dogra, S.; Carter, S.E.; Owen, N. Sit Less and Move More for Cardiovascular Health: Emerging Insights and Opportunities. Nat. Rev. Cardiol. 2021, 18, 637–648.
4. ENCODE: Encyclopedia of DNA Elements. Available online: https://www.encodeproject.org/ (accessed on 28 August 2021).
5. Reuter, J.A.; Spacek, D.V.; Snyder, M.P. High-Throughput Sequencing Technologies. Mol. Cell 2015, 58, 586–597.
6. Delihas, N. Discovery and Characterization of the First Non-Coding RNA That Regulates Gene Expression, micFRNA: A Historical Perspective. World J. Biol. Chem. 2015, 6, 272–280.
7. Ludwig, M. Non-Coding DNA Evolution: Junk DNA Revisited. Encycl. Evol. Biol. 2016, 6, 124–129.
8. Palazzo, A.F.; Lee, E.S. Non-Coding RNA: What Is Functional and What Is Junk? Front. Genet. 2015, 6, 2.
9. Ponjavic, J.; Ponting, C.P.; Lunter, G. Functionality or Transcriptional Noise? Evidence for Selection within Long Noncoding RNAs. Genome Res. 2007, 17, 556–565.
10. Mattick, J.; Makunin, I.V. Non-Coding RNA. Hum. Mol. Genet. 2006, 15, 17–29.
11. Churchman, L.S. Not Just Noise: Genomics and Genetics Bring Long Noncoding RNAs into Focus. Mol. Cell 2017, 65, 1–2.
12. Xue, Y.; Chen, R.; Qu, L.; Cao, X. Noncoding RNA: From Dark Matter to Bright Star. Sci. China Life Sci. 2020, 63, 463–468.
13. Mongelli, A.; Martelli, F.; Farsetti, A.; Gaetano, C. The Dark That Matters: Long Non-Coding RNAs as Master Regulators of Cellular Metabolism in Non-communicable Diseases. Front. Physiol. 2019, 10, 369.
14. Kaikkonen, M.U.; Lam, M.T.; Glass, C.K. Non-Coding RNAs as Regulators of Gene Expression and Epigenetics. Cardiovasc. Res. 2011, 90, 430–440.
15. Wei, J.-W.; Huang, K.; Yang, C.; Kang, C.-S. Non-Coding RNAs as Regulators in Epigenetics. Oncol. Rep. 2016, 37, 3–9.
16. Chen, Y.-C.A.; Aravin, A.A. Non-Coding RNAs in Transcriptional Regulation. Curr. Mol. Biol. Rep. 2015, 1, 10–18.
17. Patil, V.S.; Zhou, R.; Rana, T.M. Gene Regulation by Non-Coding RNAs. Crit. Rev. Biochem. Mol. Biol. 2013, 49, 16–32.
18. O'Brien, J.; Hayder, H.; Zayed, Y.; Peng, C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front. Endocrinol. 2018, 9, 402.
19. Olson, E.N. MicroRNAs as Therapeutic Targets and Biomarkers of Cardiovascular Disease. Sci. Transl. Med. 2014, 6, 239ps3.
20. Huang, W. MicroRNAs: Biomarkers, Diagnostics, and Therapeutics. Methods Mol. Biol. 2017, 1617, 57–67.
21. Gomes, C.P.; de Gonzalo-Calvo, D.; Toro, R.; Fernandes, T.; Theisen, D.; Wang, D.-Z.; Devaux, Y. Non-Coding RNAs and Exercise: Pathophysiological Role and Clinical Application in the Cardiovascular System. Clin. Sci. 2018, 132, 925–942.
22. Da Silva, G.J.; Bye, A.; el Azzouzi, H.; Wisløff, U. MicroRNAs as Important Regulators of Exercise Adaptation. Prog. Cardiovasc. Dis. 2017, 60, 130–151.
23. Altana, V.; Geretto, M.; Pulliero, A. MicroRNAs and Physical Activity. MicroRNA 2015, 4, 74–85.
24. Meurer, S.; Krüger, K.; Mooren, F. MicroRNAs unter Einfluss Körperlicher Belastung. Ger. J. Sports Med. 2016, 2016, 27–34.
25. Yao, R.; Wang, Y.; Chen, L.-L. Cellular Functions of Long Noncoding RNAs. Nat. Cell Biol. 2019, 21, 542–551.
26. Kapusta, A.; Feschotte, C. Volatile Evolution of Long Noncoding RNA Repertoires: Mechanisms and Biological Implications. Trends Genet. 2014, 30, 439–452.
27. Statello, L.; Guo, C.-J.; Chen, L.-L.; Huarte, M. Gene Regulation by Long Non-Coding RNAs and Its Biological Functions. Nat. Rev. Mol. Cell Biol. 2020, 22, 96–118.

28. Sun, M.; Kraus, W.L. From Discovery to Function: The Expanding Roles of Long Non-Coding RNAs in Physiology and Disease. Endocr. Rev. 2015, 36, 25–64.

29. Dhanoa, J.K.; Sethi, R.S.; Verma, R.; Arora, J.S.; Mukhopadhyay, C.S. Long Non-Coding RNA: Its Evolutionary Relics and Biological Implications in Mammals: A Review. J. Anim. Sci. Technol. 2018, 60, 1–10.

30. Espinosa, J.M. On the Origin of lncRNAs: Missing Link Found. Trends Genet. 2017, 33, 660–662.

31. Jarroux, J.; Morillon, A.; Pinskaya, M. History, Discovery, and Classification of lncRNAs. Adv. Exp. Med. Biol. 2017, 1008, 1–46.

32. McMullen, J.R.; Drew, B.G. Long Non-Coding RNAs (lncRNAs) in Skeletal and Cardiac Muscle: Potential Therapeutic and Diagnostic Targets? Clin. Sci. 2016, 130, 2245–2256.

33. Gomes, C.P.C.; Spencer, H.; Ford, K.L.; Michel, L.Y.M.; Baker, A.H.; Emanueli, C.; Balligand, J.-L.; Devaux, Y. The Function and Therapeutic Potential of Long Non-Coding RNAs in Cardiovascular Development and Disease. Mol. Ther.-Nucleic Acids 2017, 8, 494–507.

34. Bonilauri, B.; Dallagiovanna, B. Long Non-Coding RNAs Are Differentially Expressed after Different Exercise Training Programs. Front. Physiol. 2020, 11.

35. DiStefano, J.K. The Emerging Role of Long Noncoding RNAs in Human Disease. Methods Mol. Biol. 2018, 1706, 91–110.

36. Ismail, N.; Abdullah, N.; Murad, N.A.; Jamal, R.; Sulaiman, S. Long Non-Coding RNAs (lncRNAs) in Cardiovascular Disease Complication of Type 2 Diabetes. Diagnostics 2021, 11, 145.

37. Schmitt, A.M.; Chang, H.Y. Long Noncoding RNAs in Cancer Pathways. Cancer Cell 2016, 29, 452–463.

38. Liu, S.J.; Dang, H.X.; Lim, D.A.; Feng, F.Y.; Maher, C.A. Long Noncoding RNAs in Cancer Metastasis. Nat. Rev. Cancer 2021, 21, 446–460.

39. Ishii, N.; Ozaki, K.; Sato, H.; Mizuno, H.; Saito, S.; Takahashi, A.; Miyamoto, Y.; Ikegawa, S.; Kamatani, N.; Hori, M.; et al. Identification of a Novel Non-Coding RNA, MIAT, That Confers Risk of Myocardial Infarction. J. Hum. Genet. 2006, 51, 1087–1099.

40. Semenza, G.L. Hypoxia-Inducible Factor 1 and Cardiovascular Disease. Annu. Rev. Physiol. 2014, 76, 39–56.

41. Zhang, Y.; Zhang, L.; Wang, Y.; Ding, H.; Xue, S.; Yu, H.; Hu, L.; Qi, H.; Wang, Y.; Zhu, W.; et al. KCNQ 1 OT 1, HIF 1A-AS 2 and APOA 1-AS Are Promising Novel Biomarkers for Diagnosis of Coronary Artery Disease. Clin. Exp. Pharmacol. Physiol. 2019, 46, 635–642.

42. Jin, L.; Lin, X.; Yang, L.; Fan, X.; Wang, W.; Li, S.; Li, J.; Liu, X.; Bao, M.; Cui, X.; et al. AK098656, a Novel Vascular Smooth Muscle Cell–Dominant Long Noncoding RNA, Promotes Hypertension. Hypertension 2018, 71, 262–272.

43. Broadbent, H.M.; Peden, J.F.; Lorkowski, S.; Goel, A.; Ongen, H.; Green, F.; Clarke, R.; Collins, R.; Franzosi, M.G.; Tognoni, G.; et al. Susceptibility to Coronary Artery Disease and Diabetes Is Encoded by Distinct, Tightly Linked SNPs in the ANRIL Locus on Chromosome 9p. Hum. Mol. Genet. 2007, 17, 806–814.

44. Bayoglu, B.; Yuksel, H.; Cakmak, H.A.; Dirican, A.; Cengiz, M. Polymorphisms in the Long Non-Coding RNA CDKN2B-AS1 May Contribute to Higher Systolic Blood Pressure Levels in Hyper-Tensive Patients. Clin. Biochem. 2016, 49, 821–827.

45. Vausort, M.; Wagner, D.R.; Devaux, Y. Long Noncoding RNAs in Patients with Acute Myocardial Infarction. Circ. Res. 2014, 115, 668–677.

46. Ahmed, W.; Ali, I.S.; Riaz, M.; Younas, A.; Sadeque, A.; Niazi, A.K.; Niazi, S.H.; Ali, S.H.B.; Azam, M.; Qamar, R. Association of ANRIL Polymorphism (rs1333049:C>G) with Myocardial Infarction and Its Pharmacogenomic Role in Hypercholesterolemia. Gene 2013, 515, 416–420.

47. Shu, L.; Zhang, W.; Huang, C.; Huang, G.; Su, G.; Xu, J. lncRNA ANRIL protects H9c2 cells against hypoxia-induced injury through targeting the miR-7-5p/SIRT1 axis. J. Cell. Physiol. 2019, 235, 1175–1183.

48. Greco, S.; Zaccagnini, G.; Perfetti, A.; Fuschi, P.; Valaperta, R.; Voellenkle, C.; Castelvecchio, S.; Gaetano, C.; Finato, N.; Beltrami, A.P.; et al. Long Noncoding Rna Dysregulation in Ischemic Heart Failure. J. Transl. Med. 2016, 14, 1–14.

49. Wang, K.; Liu, C.-Y.; Zhou, L.-Y.; Wang, J.; Wang, M.; Zhao, B.; Zhao, W.-K.; Jian-Xun, W.; Yan-Fang, Z.; Zhang, X.-J.; et al. APF lncRNA Regulates Autophagy and Myocardial Infarction by Targeting miR-188-3p. Nat. Commun. 2015, 6, 6779.

50. Tang, T.-T.; Wang, B.-Q. Clinical Significance of lncRNA-AWPPH in Coronary Artery Diseases. Eur. Rev. Med. Pharmacol. Sci. 2020, 24, 11747–11751.

51. Greco, S.; Zaccagnini, G.; Fuschi, P.; Voellenkle, C.; Carrara, M.; Sadeghi, I.; Bearzi, C.; Maimone, B.; Castelvecchio, S.; Stellos, K.; et al. Increased BACE1-AS Long Noncoding RNA and β-Amyloid Levels in Heart Failure. Cardiovasc. Res. 2017, 113, 453–463.

52. Li, H.; Liu, X.; Zhang, L.; Li, X. LncRNA BANCR Facilitates Vascular Smooth Muscle Cell Proliferation and Migration through JNK Pathway. Oncotarget 2017, 8, 114568–114575.

53. Wang, K.; Long, B.; Zhou, L.-Y.; Liu, F.; Zhou, Q.-Y.; Liu, C.-Y.; Fan, Y.-Y.; Li, P.-F. CARL lncRNA Inhibits Anoxia-Induced Mitochondrial Fission and Apoptosis in Cardiomyocytes by Impairing miR-539-Dependent PHB2 Downregulation. Nat. Commun. 2014, 5, 3596.

54. Zhang, Y.; Sun, L.; Xuan, L.; Pan, Z.; Li, K.; Liu, S.; Huang, Y.; Zhao, X.; Huang, L.; Wang, Z.; et al. Reciprocal Changes of Circulating Long Non-Coding RNAs ZFAS1 and CDR1AS Predict Acute Myocardial Infarction. Sci. Rep. 2016, 6, 22384.

55. Wang, Z.; Zhang, X.-J.; Ji, Y.-X.; Zhang, P.; Deng, K.-Q.; Gong, J.; Ren, S.; Wang, X.; Chen, I.; Wang, H.; et al. The Long Noncoding RNA CHAER Defines an Epigenetic Checkpoint in Cardiac Hypertrophy. Nat. Med. 2016, 22, 1131–1139.

56. Viereck, J.; Kumarswamy, R.; Foinquinos, A.; Xiao, K.; Avramopoulos, P.; Kunz, M.; Dittrich, M.; Maetzig, T.; Zimmer, K.; Remke, J.; et al. Long Noncoding RNA CHAST Promotes Cardiac Remodeling. Sci. Transl. Med. 2016, 8, 326ra22.

57. Wang, K.; Liu, F.; Zhou, L.-Y.; Long, B.; Yuan, S.-M.; Wang, Y.; Liu, C.-Y.; Sun, T.; Zhang, X.-J.; Li, P.-F. The Long Noncoding RNA CHRF Regulates Cardiac Hypertrophy by Targeting miR-489. Circ. Res. 2014, 114, 1377–1388.

58. Hennessy, E.J.; Van Solingen, C.; Scacalossi, K.R.; Ouimet, M.; Afonso, M.S.; Prins, J.; Koelwyn, G.J.; Sharma, M.; Ramkhelawon, B.; Carpenter, S.; et al. The Long Noncoding RNA CHROME Regulates Cholesterol Homeostasis in Primates. Nat. Metab. 2018, 1, 98–110.

59. Yang, Y.; Cai, Y.; Wu, G.; Chen, X.; Liu, Y.; Wang, X.; Yu, J.; Li, C.; Chen, X.; Jose, P.A.; et al. Plasma Long Non-Coding RNA, CoroMarker, a Novel Biomarker for Diagnosis of Coronary Artery Disease. Clin. Sci. 2015, 129, 675–685.

60. Long, B.; Li, N.; Xu, X.-X.; Li, X.-X.; Xu, X.-J.; Guo, D.; Zhang, D.; Wu, Z.-H.; Zhang, S.-Y. Long Noncoding RNA FTX Regulates Cardiomyocyte Apoptosis by Targeting miR-29b-1-5p and Bcl2l2. Biochem. Biophys. Res. Commun. 2018, 495, 312–318.

61. Wang, Y.-N.; Shan, K.; Yao, M.-D.; Yao, J.; Wang, J.-J.; Li, X.; Liu, B.; Zhang, Y.-Y.; Ji, Y.; Jiang, Q.; et al. Long Noncoding RNA-GAS5: A Novel Regulator of Hypertension-Induced Vascular Remodeling. Hypertension 2016, 68, 736–748.

62. Liu, K.; Liu, C.; Zhang, Z. lncRNA GAS5 Acts as a ceRNA for miR-21 in Suppressing PDGF-BB-Induced Proliferation and Migration in Vascular Smooth Muscle Cells. J. Cell. Biochem. 2019, 120, 15233–15240.

63. Du, J.; Yang, S.-T.; Liu, J.; Zhang, K.-X.; Leng, J.-Y. Silence of LncRNA GAS5 Protects Cardiomyocytes H9c2 against Hypoxic Injury via Sponging miR-142-5p. Mol. Cells 2019, 42, 397–405.

64. Zhang, Y.; Hou, Y.-M.; Gao, F.; Xiao, J.-W.; Li, C.-C.; Tang, Y. lncRNA GAS5 Regulates Myocardial Infarction by Targeting the miR-525-5p/CALM2 Axis. J. Cell. Biochem. 2019, 120, 18678–18688.

65. Hao, S.; Liu, X.; Sui, X.; Pei, Y.; Liang, Z.; Zhou, N. Long Non-Coding RNA GAS5 Reduces Cardiomyocyte Apoptosis Induced by MI through sema3a. Int. J. Biol. Macromol. 2018, 120, 371–377.

66. Das, S.; Zhang, E.; Senapati, P.; Amaram, V.; Reddy, M.A.; Stapleton, K.; Leung, A.; Lanting, L.; Wang, M.; Chen, Z.; et al. A Novel Angiotensin II–Induced Long Noncoding RNA Giver Regulates Oxidative Stress, Inflammation, and Proliferation in Vascular Smooth Muscle Cells. Circ. Res. 2018, 123, 1298–1312.

67. Zhou, M.; Zou, Y.-G.; Xue, Y.-Z.; Wang, X.-H.; Gao, H.; Dong, H.-W.; Zhang, Q. Long Non-Coding RNA H19 Protects Acute Myocardial Infarction through Activating Autophagy in Mice. Eur. Rev. Med. Pharmacol. Sci. 2018, 22, 5647–5651.

68. Choong, O.K.; Chen, C.-Y.; Zhang, J.; Lin, J.-H.; Lin, P.-J.; Ruan, S.-C.; Kamp, T.J.; Hsieh, P.C. Hypoxia-Induced H19/YB-1 Cascade Modulates Cardiac Remodeling after Infarction. Theranostics 2019, 9, 6550–6567.

69. Wang, X.-M.; Li, X.-M.; Song, N.; Zhai, H.; Gao, X.-M.; Yang, Y.-N. Long Non-Coding RNAs H19, MALAT1 and MIAT as Potential Novel Biomarkers for Diagnosis of Acute Myocardial Infarction. Biomed. Pharmacother. 2019, 118, 109208.

70. Yao, Y.; Xiong, G.; Jiang, X.; Song, T. The Overexpression of lncRNA H19 as a Diagnostic Marker for Coronary Artery Disease. Rev. Assoc. Med. Bras. 2019, 65, 110–117.

71. Gao, W.; Zhu, M.; Wang, H.; Zhao, S.; Zhao, D.; Yang, Y.; Wang, Z.-M.; Wang, F.; Yang, Z.-J.; Lu, X.; et al. Association of Polymorphisms in Long Non-Coding RNA H19 with Coronary Artery Disease Risk in a Chinese Population. Mutat. Res. Mol. Mech. Mutagen. 2015, 772, 15–22.

72. Liu, L.; An, X.; Li, Z.; Song, Y.; Li, L.; Zuo, S.; Liu, N.; Yang, G.; Wang, H.; Cheng, X.; et al. The H19 Long Noncoding RNA Is a Novel Negative Regulator of Cardiomyocyte Hypertrophy. Cardiovasc. Res. 2016, 111, 56–65.

73. Boeckel, J.-N.; Perret, M.F.; Glaser, S.F.; Seeger, T.; Heumüller, A.W.; Chen, W.; John, D.; Kokot, K.E.; Katus, H.A.; Haas, J.; et al. Identification and Regulation of the Long Non-Coding RNA Heat2 in Heart Failure. J. Mol. Cell. Cardiol. 2019, 126, 13–22.

74. Gao, L.; Liu, Y.; Guo, S.; Yao, R.; Wu, L.; Xiao, L.; Wang, Z.; Liu, Y.; Zhang, Y. Circulating Long Noncoding RNA HOTAIR is an Essential Mediator of Acute Myocardial Infarction. Cell. Physiol. Biochem. 2017, 44, 1497–1508.

75. Liao, B.; Chen, R.; Lin, F.; Mai, A.; Chen, J.; Li, H.; Xu, Z.; Dong, S. Long Noncoding RNA HOTTIP Promotes Endothelial Cell Proliferation and Migration via Activation of the Wnt/β-Catenin Pathway. J. Cell. Biochem. 2017, 119, 2797–2805.

76. Devaux, Y.; Creemers, E.E.; Boon, R.A.; Werfel, S.; Thum, T.; Engelhardt, S.; Dimmeler, S.; Squire, I. Circular RNAs in Heart Failure. Eur. J. Hear. Fail. 2017, 19, 701–709.

77. Kumarswamy, R.; Bauters, C.; Volkmann, I.; Maury, F.; Fetisch, J.; Holzmann, A.; Lemesle, G.; de Groote, P.; Pinet, F.; Thum, T. Circulating Long Noncoding RNA, LIPCAR, Predicts Survival in Patients with Heart Failure. Circ. Res. 2014, 114, 1569–1575.

78. Zhang, Z.; Gao, W.; Long, Q.-Q.; Zhang, J.; Lian-Sheng, W.; Liu, D.-C.; Yan, J.-J.; Yang, Z.-J.; Wang, L.-S. Increased Plasma Levels of lncRNA H19 and LIPCAR Are Associated with Increased Risk of Coronary Artery Disease in a Chinese Population. Sci. Rep. 2017, 7, 1–9.

79. Huarte, M.; Guttman, M.; Feldser, D.; Garber, M.; Koziol, M.J.; Kenzelmann-Broz, D.; Khalil, A.M.; Zuk, O.; Amit, I.; Rabani, M.; et al. A Large Intergenic Noncoding RNA Induced by p53 Mediates Global Gene Repression in the p53 Response. Cell 2010, 142, 409–419.

80. Tang, S.-S.; Cheng, J.; Cai, M.-Y.; Yang, X.-L.; Liu, X.G.; Zheng, B.-Y.; Xiong, X.-D. Association of lincRNA-p21Haplotype with Coronary Artery Disease in a Chinese Han Population. Dis. Markers 2016, 2016, 1–7.

81. Wang, X.; Zhao, Z.; Zhang, W.; Wang, Y. Long Noncoding RNA LINC00968 Promotes Endothelial Cell Proliferation and Migration via Regulating miR-9-3p Expression. J. Cell. Biochem. 2019, 120, 8214–8221.

82. Jiang, F.; Zhou, X.; Huang, J. Long Non-Coding RNA-ROR Mediates the Reprogramming in Cardiac Hypertrophy. PLoS ONE 2016, 11, e0152767.

83. Leung, A.; Trac, C.; Jin, W.; Lanting, L.; Akbany, A.; Sætrom, P.; Schones, D.E.; Natarajan, R. Novel Long Noncoding RNAs Are Regulated by Angiotensin II in Vascular Smooth Muscle Cells. Circ. Res. 2013, 113, 266–278.

84. Chen, G.; Huang, S.; Song, F.; Zhou, Y.; He, X. Lnc-Ang362 Is a Pro-Fibrotic Long Non-Coding RNA Promoting Cardiac Fibrosis after Myocardial Infarction by Suppressing Smad7. Arch. Biochem. Biophys. 2020, 685, 108354.

85. Guo, X.; Wu, X.; Han, Y.; Tian, E.; Cheng, J. LncRNA MALAT1 Protects Cardiomyocytes from Isoproterenol-Induced Apoptosis through Sponging miR-558 to Enhance ULK1-Mediated Protective Autophagy. J. Cell. Physiol. 2018, 234, 10842–10854.

86. Hu, L.; Xu, Y.-N.; Wang, Q.; Liu, M.-J.; Zhang, P.; Zhao, L.-T.; Liu, F.; Zhao, D.-Y.; Pei, H.-N.; Yao, X.-B.; et al. Aerobic Exercise Improves Cardiac Function in Rats with Chronic Heart Failure through Inhibition of the Long Non-Coding RNA Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1). Ann. Transl. Med. 2021, 9, 340.

87. Toraih, E.; El-Wazir, A.; Alghamdi, S.A.; Alhazmi, A.S.; El-Wazir, M.; Abdel-Daim, M.; Fawzy, M.S. Association of Long Non-Coding RNA MIAT and MALAT1 Expression Profiles in Peripheral Blood of Coronary Artery Disease Patients with Previous Cardiac Events. Genet. Mol. Biol. 2019, 42, 509–518.

88. Wang, K.; Sun, T.; Li, N.; Wang, Y.; Wang, J.; Zhou, L.-Y.; Long, B.; Liu, C.-Y.; Liu, F.; Li, P.-F. MDRL lncRNA Regulates the Processing of miR-484 Primary Transcript by Targeting miR-361. PLoS Genet. 2014, 10, e1004467.

89. Wu, H.; Zhao, Z.-A.; Liu, J.; Hao, K.; Yu, Y.; Han, X.; Li, J.; Wang, Y.; Lei, W.; Dong, N.; et al. Long Noncoding RNA Meg3 Regulates Cardiomyocyte Apoptosis in Myocardial Infarction. Gene Ther. 2018, 25, 511–523.

90. Piccoli, M.-T.; Gupta, S.K.; Viereck, J.; Foinquinos, A.; Samolovac, S.; Kramer, F.L.; Garg, A.; Remke, J.; Zimmer, K.; Batkai, S.; et al. Inhibition of the Cardiac Fibroblast–Enriched lncRNA Meg3 Prevents Cardiac Fibrosis and Diastolic Dysfunction. Circ. Res. 2017, 121, 575–583.

91. Zhang, J.; Gao, C.; Meng, M.; Tang, H. Long Noncoding RNA MHRT Protects Cardiomyocytes against H2O2-Induced Apoptosis. Biomol. Ther. 2016, 24, 19–24.

92. Han, P.; Li, W.; Lin, C.-H.; Yang, J.; Shang, C.; Nuernberg, S.T.; Jin, K.K.; Xu, W.; Lin, C.-Y.; Lin, C.-J.; et al. A Long Noncoding Rna Protects the Heart from Pathological Hypertrophy. Nat. Cell Biol. 2014, 514, 102–106.

93. Xuan, L.; Sun, L.; Zhang, Y.; Huang, Y.; Hou, Y.; Li, Q.; Guo, Y.; Feng, B.; Cui, L.; Wang, X.; et al. Circulating Long Non-Coding Rnas Nron and MHRT as Novel Predictive Biomarkers of Heart Failure. J. Cell. Mol. Med. 2017, 21, 1803–1814.

94. Qu, X.; Du, Y.; Shu, Y.; Gao, M.; Sun, F.; Luo, S.; Yang, T.; Zhan, L.; Yuan, Y.; Chu, W.; et al. MIAT Is a Pro-Fibrotic Long Non-Coding RNA Governing Cardiac Fibrosis in Post-Infarct Myocardium. Sci. Rep. 2017, 7, srep42657.

95. Zhu, X.-H.; Yuan, Y.-X.; Rao, S.-L.; Wang, P. LncRNA MIAT Enhances Cardiac Hypertrophy Partly through Sponging miR-150. Eur. Rev. Med. Pharmacol. Sci. 2016, 20, 3653.

96. Zangrando, J.; Zhang, L.; Vausort, M.; Maskali, F.; Marie, P.-Y.; Wagner, D.R.; Devaux, Y. Identification of Candidate Long Non-Coding RNAs in Response to Myocardial Infarction. BMC Genom. 2014, 15, 460.

97. Wang, X.; Yong, C.; Yu, K.; Yu, R.; Zhang, R.; Yu, L.; Li, S.; Cai, S. Long Noncoding RNA (lncRNA) n379519 Promotes Cardiac Fibrosis in Post-Infarct Myocardium by Targeting miR-30. Med. Sci. Monit. 2018, 24, 3958–3965.

98. Hu, Y.-W.; Guo, F.-X.; Xu, Y.-J.; Li, P.; Lu, Z.-F.; McVey, D.G.; Zheng, L.; Wang, Q.; Ye, J.; Kang, C.-M.; et al. Long Noncoding RNA NEXN-AS1 Mitigates Atherosclerosis by Regulating the Actin-Binding Protein NEXN. J. Clin. Investig. 2019, 129, 1115–1128.

99. Tu, G.; Zou, L.; Liu, S.; Wu, B.; Lv, Q.; Wang, S.; Xue, Y.; Zhang, C.; Yi, Z.; Zhang, X.; et al. Long Noncoding NONRATT021972 siRNA Normalized Abnormal Sympathetic Activity Mediated by the Upregulation of P2X7 Receptor in Superior Cervical Ganglia after Myocardial Ischemia. Purinergic Signal. 2016, 12, 521–535.

100. Chen, S.; Chen, R.; Zhang, T.; Lin, S.; Chen, Z.; Zhao, B.; Li, H.; Wu, S. Relationship of Cardiovascular Disease Risk Factors and Noncoding RNAs with Hypertension: A Case-Control Study. BMC Cardiovasc. Disord. 2018, 18, 58.

101. Wang, K.; Liu, F.; Liu, C.-Y.; An, T.; Zhang, J.; Zhou, L.-Y.; Wang, M.; Dong, Y.-H.; Li, N.; Gao, J.-N.; et al. The Long Noncoding RNA NRF Regulates Programmed Necrosis and Myocardial Injury during Ischemia and Reperfusion by Targeting miR-873. Cell Death Differ. 2016, 23, 1394–1405.

102. Sun, F.; Zhuang, Y.; Zhu, H.; Wu, H.; Li, D.; Zhan, L.; Yang, W.; Yuan, Y.; Xie, Y.; Yang, S.; et al. LncRNA PCFL Promotes Cardiac Fibrosis via miR-378/GRB2 Pathway Following Myocardial Infarction. J. Mol. Cell. Cardiol. 2019, 133, 188–198.

103. Ballantyne, M.D.; Pinel, K.; Dakin, R.S.; Vesey, A.T.; Diver, L.; MacKenzie, R.M.; Garcia, R.; Welsh, P.; Sattar, N.A.; Hamilton, G.; et al. Smooth Muscle Enriched Long Noncoding RNA (SMILR) Regulates Cell Proliferation. Circulation 2016, 133, 2050–2065.

104. Huang, S.; Tao, W.; Guo, Z.; Cao, J.; Huang, X. Suppression of Long Noncoding RNA TTTY15 Attenuates Hypoxia-Induced Cardiomyocytes Injury by Targeting miR-455-5p. Gene 2019, 701, 1–8.

105. Chen, J.; Hu, Q.; Zhang, B.-F.; Liu, X.-P.; Yang, S.; Jiang, H. Long Noncoding RNA UCA1 Inhibits Ischaemia/Reperfusion Injury Induced Cardiomyocytes Apoptosis via Suppression of Endoplasmic Reticulum Stress. Genes Genom. 2019, 41, 803–810.

106. Yan, Y.; Zhang, B.; Liu, N.; Qi, C.; Xiao, Y.; Tian, X.; Li, T.; Liu, B. Circulating Long Noncoding RNA UCA1 as a Novel Biomarker of Acute Myocardial Infarction. BioMed Res. Int. 2016, 2016, 1–7.

107. Zhang, J.; Yu, L.; Xu, Y.; Liu, Y.; Li, Z.; Xue, X.; Wan, S.; Wang, H. Long Noncoding RNA Upregulated in Hypothermia Treated Cardiomyocytes Protects against Myocardial Infarction through Improving Mitochondrial Function. Int. J. Cardiol. 2018, 266, 213–217.

108. Micheletti, R.; Plaisance, I.; Abraham, B.J.; Sarre, A.; Ting, C.-C.; Alexanian, M.; Maric, D.; Maison, D.; Nemir, M.; Young, R.A.; et al. The Long Noncoding RNA Wisper Controls Cardiac Fibrosis and Remodeling. Sci. Transl. Med. 2017, 9, eaai9118.

109. Jiao, L.; Li, M.; Shao, Y.; Zhang, Y.; Gong, M.; Yang, X.; Wang, Y.; Tan, Z.; Sun, L.; Xuan, L.; et al. lncRNA-ZFAS1 Induces Mitochondria-Mediated Apoptosis by Causing Cytosolic Ca2+ Overload in Myocardial Infarction Mice Model. Cell Death Dis. 2019, 10, 1–12.

110. Yeh, C.-F.; Chang, Y.-C.E.; Lu, C.-Y.; Hsuan, C.-F.; Chang, W.-T.; Yang, K.-C. Expedition to the Missing Link: Long Noncoding RNAs in Cardiovascular Diseases. J. Biomed. Sci. 2020, 27, 1–16.

111. Uchida, S.; Dimmeler, S. Long Noncoding RNAs in Cardiovascular Diseases. Circ. Res. 2015, 116, 737–750.

112. Greco, S.; Somoza, A.S.; Devaux, Y.; Martelli, F. Long Noncoding RNAs and Cardiac Disease. Antioxidants Redox Signal. 2018, 29, 880–901.

113. Hobuß, L.; Bär, C.; Thum, T. Long Non-Coding RNAs: At the Heart of Cardiac Dysfunction? Front. Physiol. 2019, 10, 30.

114. Fang, Y.; Xu, Y.; Wang, R.; Hu, L.; Guo, D.; Xue, F.; Guo, W.; Zhang, D.; Hu, J.; Li, Y.; et al. Recent Advances on the Roles of LncRNAs in Cardiovascular Disease. J. Cell. Mol. Med. 2020, 24, 12246–12257.
115. Collins, L.; Binder, P.; Chen, H.; Wang, X. Regulation of Long Non-Coding RNAs and MicroRNAs in Heart Disease: Insight into Mechanisms and Therapeutic Approaches. Front. Physiol. 2020, 11, 798.
116. Viereck, J.; Thum, T. Circulating Noncoding RNAs as Biomarkers of Cardiovascular Disease and Injury. Circ. Res. 2017, 120, 381–399.
117. Poller, W.; Dimmeler, S.; Heymans, S.; Zeller, T.; Haas, J.; Karakas, M.; Leistner, D.; Jakob, P.; Nakagawa, S.; Blankenberg, S.; et al. Non-Coding RNAs in Cardiovascular Diseases: Diagnostic and Therapeutic Perspectives. Eur. Hear. J. 2017, 39, 2704–2716.
118. Moldovan, L.; Batte, K.E.; Trgovcich, J.; Wisler, J.; Marsh, C.B.; Piper, M. Methodological Challenges in Utilizing Mi RNAs as Circulating Biomarkers. J. Cell. Mol. Med. 2014, 18, 371–390.
119. Kitow, J.; Derda, A.A.; Beermann, J.; Kumarswarmy, R.; Pfanne, A.; Fendrich, J.; Lorenzen, J.M.; Xiao, K.; Bavendiek, U.; Bauersachs, J.; et al. Mitochondrial Long Noncoding RNAs as Blood Based Biomarkers for Cardiac Remodeling in Patients with Hypertrophic Cardiomyopathy. Am. J. Physiol. Heart Circ. Physiol. 2016, 311, 707–712.
120. Li, D.; Chen, G.; Yang, J.; Fan, X.; Gong, Y.; Xu, G.; Cui, Q.; Geng, B. Transcriptome Analysis Reveals Distinct Patterns of Long Noncoding RNAs in Heart and Plasma of Mice with Heart Failure. PLoS ONE 2013, 8, e77938.
121. Goretti, E.; Wagner, D.R.; Devaux, Y. Mirnas as Biomarkers of Myocardial Infarction: A Step Forward towards Personalized Medicine? Trends Mol. Med. 2014, 20, 716–725.
122. Congrains, A.; Kamide, K.; Oguro, R.; Yasuda, O.; Miyata, K.; Yamamoto, E.; Kawai, T.; Kusunoki, H.; Yamamoto, H.; Takeya, Y.; et al. Genetic Variants at the 9p21 Locus Contribute to Atherosclerosis through Modulation of ANRIL and CDKN2A/B. Atherosclerosis 2012, 220, 449–455.
123. Iacobucci, I.; Sazzini, M.; Garagnani, P.; Ferrari, A.; Boattini, A.; Lonetti, A.; Papayannidis, C.; Mantovani, V.; Marasco, E.; Ottaviani, E.; et al. A Polymorphism in the Chromosome 9p21 ANRIL Locus Is Associated to Philadelphia Positive Acute Lymphoblastic Leukemia. Leuk. Res. 2011, 35, 1052–1059.
124. Diederichs, S. The Four Dimensions of Noncoding RNA Conservation. Trends Genet. 2014, 30, 121–123.
125. Spitale, R.C.; Crisalli, P.; Flynn, R.A.; Torre, E.A.; Kool, E.T.; Chang, H.Y. RNA SHAPE Analysis in Living Cells. Nat. Chem. Biol. 2013, 9, 18–20.
126. Ding, Y.; Tang, Y.; Kwok, C.K.; Zhang, Y.; Bevilacqua, P.C.; Assmann, S.M. In Vivo Genome-Wide Profiling of RNA Secondary Structure Reveals Novel Regulatory Features. Nature 2014, 505, 696–700.
127. Das, S.; Shah, R.; Dimmeler, S.; Freedman, J.E.; Holley, C.; Lee, J.-M.; Moore, K.; Musunuru, K.; Wang, D.-Z.; Xiao, J.; et al. Noncoding RNAs in Cardiovascular Disease: Current Knowledge, Tools and Technologies for Investigation, and Future Directions: A Scientific Statement from the American Heart Association. Circ. Genom. Precis. Med. 2020, 13.
128. Volders, P.-J.; Anckaert, J.; Verheggen, K.; Nuytens, J.; Martens, L.; Mestdagh, P.; Vandesompele, J. LNCipedia 5: Towards a Reference Set of Human Long Non-Coding RNAs. Nucleic Acids Res. 2019, 47, 135–139.
129. Li, J.; Ma, W.; Zeng, P.; Wang, J.; Geng, B.; Yang, J.; Cui, Q. LncTar: A Tool for Predicting the RNA Targets of Long Noncoding RNAs. Brief. Bioinform. 2014, 16, 806–812.
130. Ma, L.; Li, A.; Zou, D.; Xu, X.; Xia, L.; Yu, J.; Bajic, V.B.; Zhang, Z. LncRNAWiki: Harnessing Community Knowledge in Collaborative Curation of Human Long Non-Coding RNAs. Nucleic Acids Res. 2014, 43, 187–192.
131. Ma, L.; Cao, J.; Liu, L.; Li, Z.; Shireen, H.; Pervaiz, N.; Batool, F.; Raza, R.Z.; Zou, D.; Bao, Y.; et al. Community Curation and Expert Curation of Human Long Noncoding RNAs with LncRNAWiki and LncBook. Curr. Protoc. Bioinform. 2019, 67, e82.