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Long non-coding RNAs in the failing heart and vasculature

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ABSTRACT

Following completion of the human genome, it became evident that the majority of our DNA is transcribed into non-coding RNAs (ncRNAs) instead of protein-coding messenger RNA. Deciphering the function of these ncRNAs, including both small- and long ncRNAs (lncRNAs), is an emerging field of research. LncRNAs have been associated with many disorders and a number have been identified as key regulators in the development and progression of disease, including cardiovascular disease (CVD). CVD causes millions of deaths worldwide, annually. Risk factors include coronary artery disease, high blood pressure and ageing. In this review, we will focus on the roles of lncRNAs in the cellular and molecular processes that underlie the development of CVD: cardiomyocyte hypertrophy, fibrosis, inflammation, vascular disease and ageing. Finally, we discuss the biomarker and therapeutic potential of lncRNAs.

1. Introduction

1.1. Non-coding RNAs in cardiovascular disease

Cardiovascular disease (CVD) accounts for the greatest proportion of the mortality rate worldwide, with more than 17 million fatalities attributed to it annually [1]. CVD is complex and includes disorders of the heart and blood vessels. Heart failure (HF) can develop after a myocardial infarction (MI), myocarditis, valvular disease, or hypertension [2]. Moreover, coronary artery disease as a result of chronic inflammation of the vessels, vascular calcification and atherosclerosis, is one of the main risk factors for HF [3]. The heart responds to these pathological challenges through a series of molecular and cellular changes, collectively referred to as cardiac remodelling [4]. Four main processes are involved in the pathophysiology of cardiac remodelling: hypertrophy, fibrosis, inflammation, and vascular disease. However, ageing might be the most important factor contributing to cardiac remodelling and the development of CVD [5,6].

In the past decades, considerable research has been conducted with patients, in animals, and at the cellular level, with the main focus on protein-coding genes and their transcribed messenger RNA (mRNA) and translated proteins. However, in the current post-genomic era, we know that only 2% of the human genome is transcribed into protein-coding genes, leaving the majority undefined (International Human Genome Sequencing Consortium 2004). In the last 15 years, studies also started to focus on the remaining 98% of the genome and found that up to 90% is being transcribed into RNA (non-coding RNAs) [7]. Non-coding RNAs (ncRNAs) can differ in length, from small ncRNAs of less than 200 nucleotides, for example microRNAs (miRNAs), to large ncRNAs with over 200 nucleotides named long ncRNAs (lncRNAs). miRNAs have been described as playing significant roles in cancer development [8], prognosis [9–13], neuronal disorders [14,15], and have central roles in CVD development [16–20]. LncRNAs research only recently came to prominence, with the first functional studies in the early 1990s [21–23]. Although the first studies examining the role of lncRNAs in the heart were published in 2012, these studies focussed primarily on cardiac development [24,25]. In this review, we discuss the latest literature concerning the role of lncRNAs in CVD and its associated risk factors.

1.2. Classification

In general, lncRNAs are defined as ncRNAs that have a length >200 nucleotides, excluding the known classic ribosomal RNAs

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[26]. Amaral et al. proposed a slightly different definition: lncRNAs are ncRNAs that may function as either primary or spliced transcripts, independent of small RNAs, excluding the structural RNAs (ribosomal RNA). Here, the length of the lncRNA is not specified as one of the criteria [27]. Therefore, there are also ncRNAs, such as *BC1* and *snaR,* which are actually shorter, yet are still classified as lncRNAs [28,29].

Even though they lack an open reading frame and do not encode for proteins, there are many similarities between lncRNAs and protein-coding genes. Both are transcribed by RNA polymerase II or III, many are 5′-capped, 3′-end poly-adenylated, and multi-exonic [30,31]. LncRNAs can regulate gene expression at the transcriptional, as well as the post-transcriptional level [32]. However, classifying lncRNAs in defined subgroups remains challenging. In general, lncRNAs exhibit poorer conservation than protein-coding genes [33]. Most lncRNAs will be folded after transcription and create a tertiary structure [34]. It is suggested that this tertiary structure, and not so much their sequence composition, determines their function [35]. Still, recognizing and classifying the structure of lncRNAs remains in its infancy and therefore other classification methods have been proposed.

LncRNAs can be classified according to their features: by their effect on DNA sequences, by their mechanisms of function (transcriptional regulation, post-transcriptional regulation, or other functions), by their targeting mechanism (based on the types of interactions they make with their targets, and the consequences of these actions), and most commonly, by their genomic location [32]. Based on their genomic location, lncRNAs can be classified as: (1) sense, transcribed from the same strand and the same direction as the surrounding protein-coding genes, they can be both (multi-) exonic and intronic; (2) antisense, transcribed from the opposite strand of surrounding protein-coding genes, also with the possibility of being both (multi-)exonic and intronic; (3) intronic, located entirely in intronic regions of a protein-coding gene; (4) intergenic, located in between two protein-coding genes, transcribed in the same direction; (5) bidirectional, located within 1 kb of the promoter region of a protein-coding gene, but transcribed from the opposite strand (Fig. 1).

1.3. Mode of action of lncRNAs

Given that lncRNAs have only recently been described, knowledge about their mechanism of action remains limited. By contrast, miRNAs have been studied for many years now and have a clear mode of action: they act by targeting mRNAs in a sequence specific manner and, in this way, repress translation and/or promote degradation of the target mRNA [9]. Based on the expanding knowledge about their cellular function, lncRNAs can be divided into several functional categories: signal, decoy, guide, scaffold, enhancer, and circular lncRNAs (Fig. 2) [36].

Signal lncRNAs are only expressed at specific time points and they are localized to certain subcellular regions where they exert their function, for example during development. They can be cell type-specific, and they respond to various stimuli [37]. *KCNQ1OT1* and *AIR* are two lncRNAs that mediate transcription at specific time points during early development, by interacting with chromatin-modifying enzymes [38,39]. Therefore, these signal lncRNAs could also be classified as scaffold or decoy lncRNAs. Decoy lncRNAs bind to regulatory factors such as transcription factors, RNA-binding proteins, and chromatin modifiers, altering their biological activity [37]. As an example, *telomeric repeat-containing RNA* (*TERRA*) can bind directly to telomerase reverse transcriptase, an enzyme which is part of the telomerase complex, and inhibit its function [40,41]. *Metastasis associated in lung adenocarcinoma transcript 1* (*Malat1*) is another lncRNA which can be categorized as a decoy lncRNA, as it localizes to nuclear speckles where it sequesters splicing factors and thereby affects alternative splicing for a number of pre-mRNAs [42]. In addition, according to the competing endogenous RNA (ceRNA) hypothesis, lncRNAs can function as sponges for certain miRNAs [43]. In this setting, lncRNAs bind to miRNAs and influence the protein translation of the target mRNAs.

There are numerous lncRNAs that have been shown to target miRNAs and in this way affect cellular mechanisms underlying disease [44–48]. Guide lncRNAs regulate gene activation or repression by forming ribonucleoprotein complexes and mediating their localization to specific target sites [37]. Comparable to guide lncRNAs are scaffold lncRNAs which can form similar structures, although they affect the molecular components of the complex itself. Several studies have shown effects of lncRNAs on chromatin complexes and histone modifiers [49,50]. However, whether these are scaffold or guide lncRNAs remains elusive. An alternative mechanism of action has been described, in which enhancer lncRNAs are produced from enhancer elements and influence the activation of target genes [51]. These lncRNAs have been shown to play important regulatory roles, for example in oestrogen-dependent transcriptional activation [52].

A fairly new class of ncRNAs, referred to as circular RNAs, are generated by backsplicing of the 5′ and 3′ ends of a produced RNA, and thereby forming a loop. Due to their circularity, they are very stable and resistant to digestion by exonucleases. They can interfere with RNA processing, regulate splicing, act as miRNA sponges [53], and have been implicated in disease processes (recently reviewed by Green et al.) [54]. It is debatable whether circular RNAs should be regarded as lncRNAs, or are a different and separate class of ncRNAs. Circular RNAs can have different lengths, ranging from under 100 nucleotides to over 4 kb. In addition, they can be transcribed from the same genomic region as their co-existing lncRNA [54]. For example, multiple RNA transcripts can be transcribed from the INK4/ARF locus including the linear lncRNA *ANRIL* and separate circular RNAs [55]. Therefore, when considering the semantics, it seems to make most sense to classify circular RNAs as a separate class of ncRNAs. Still, the functions of circular RNAs might overlap with those of lncRNAs.

The classification of lncRNAs remains cumbersome and sometimes arbitrary, given for instance that they can be intronic and intergenic at the same time, and can function as decoy and scaffold RNAs simultaneously. Improving knowledge on the tertiary structure of lncRNAs may help to enhance understanding of the function of lncRNAs. This could aid in finding binding partners of lncRNAs and identifying in which molecular pathways they are involved. In addition, knowledge on their tertiary structure will improve the design of tools to knockdown specific lncRNAs and in this way affect cellular processes involved in disease. Another classification system that is successfully used for proteins is subcellular localization. Indeed, cellular fractions have already been subjected to RNA sequencing in order to link nuclear- or whole cell localization of lncRNAs with particular functions [56]. Studying their subcellular localization and investigating their interactions with proteins will enhance knowledge about their functions. A broad overview of different techniques to investigate the function of lncRNAs is described by Kashi et al. [57]. This article shows that we might have to reconsider the current classification system and try to improve it or change it completely by concentrating on lncRNAs structure, cellular localization, and binding partners.

2. LncRNAs in cardiomyocyte hypertrophy

2.1. Cardiac hypertrophic cell signalling

Cardiomyocyte growth (hypertrophy) can be induced by

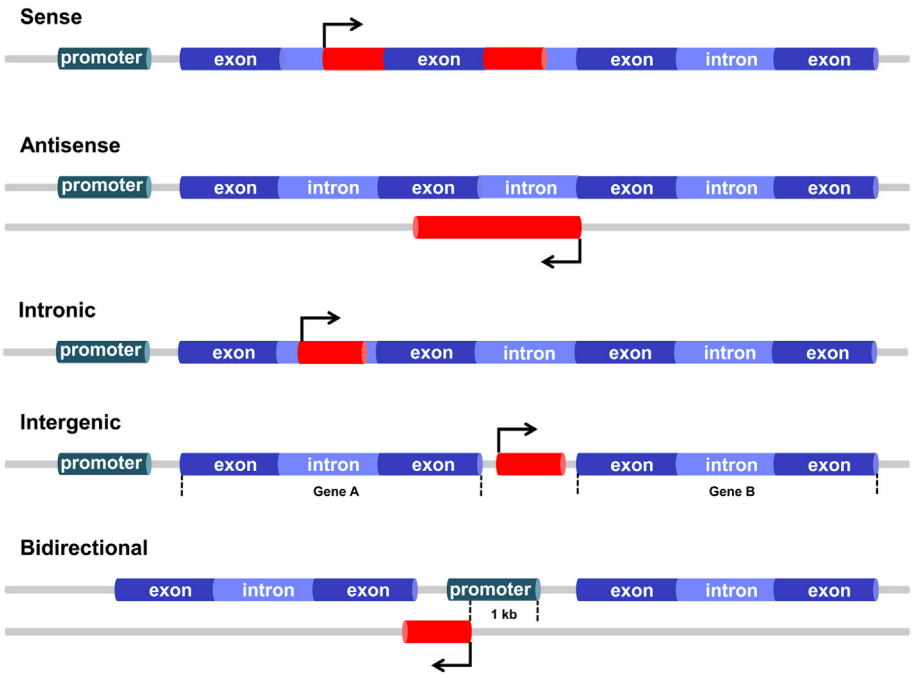

Fig. 1. Classification of lncRNAs based on their genomic location. Sense lncRNAs are transcribed from the same strand and in the same direction as their surrounding protein-coding genes; they can be both (multi-)exonic and intronic. Antisense lncRNAs are transcribed from the opposite strand of the protein-coding genes and can also be both (mulit-)exonic and intronic. Intronic lncRNAs are located entirely in intronic regions of a protein-coding gene. Intergenic lncRNAs are located in between two protein-coding genes, and are transcribed in the same direction. Bidirectional lncRNas are located within 1 kb of the promoter region of a protein-coding gene, but are transcribed from the opposite strand.

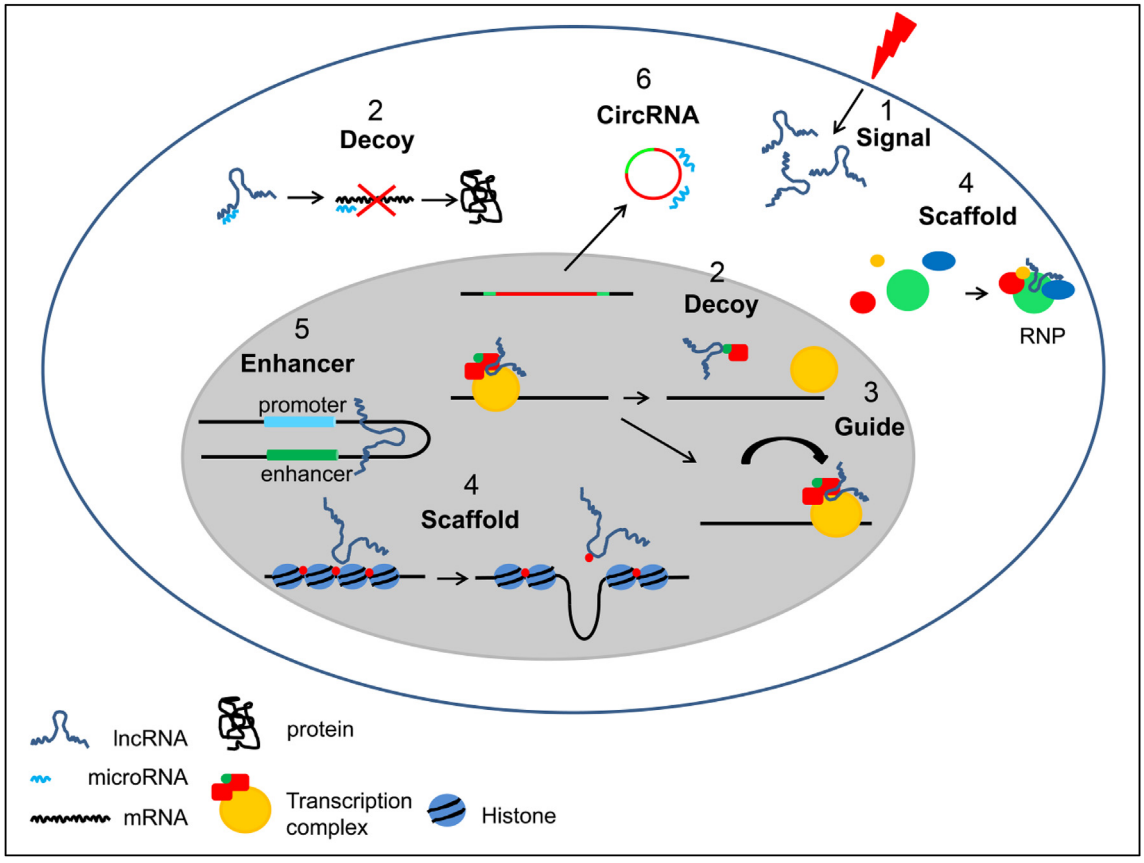

Fig. 2. Functions of lncRNAs. 1) Signal lncRNAs are only expressed at specific time points and at specific locations in the cell. 2) Decoy lncRNAs can bind to regulatory factors and microRNAs, and alter their function. 3) Guide lncRNAs regulate gene activation or repression by relocalization of the ribonucleoprotein complex. 4) Scaffold lncRNAs can form similar structures as guide lncRNAs, but they affect the molecular components of the complex itself. 5) Enhancer lncRNAs are produced from enhancer elements and influence the activation of target genes. 6) Circular lncRNAs can interfere with RNA processing, RNA splicing and can act as microRNA sponges.

biomechanical or neurohumoural mechanisms. These processes can be triggered by pathological stimuli, including chronic hypertension, ischaemic disease, viral myocarditis, diabetic cardiomyopathy, or familial cardiomyopathy [58,59]. Cardiomyocyte hypertrophy is a cellular process involving many different signalling pathways (extensively reviewed by Heineke and Molkentin) [60]. In short, cardiomyocytes sense neurohumoral and endocrine hormones such as catecholamines, endothelin-1 (Et-1), angiotensin II (AngII), insulin-like growth factor-I, and cytokines by their membrane-bound (G-protein-coupled) receptors and activate their intracellular signalling pathways [60]. The major signalling pathways described in literature today, include mitogen-activated protein kinase (MAPK), calcineurin–nuclear factor of activated T cells (NFAT), phosphatidylinositol 3-kinase-AKT, Janus kinase (JAK) - signal transducer and activator of transcription (STAT), and chromatin remodelling by histone deacetylases (HDACs) [61–64]. Activation of all these pathways eventually leads to activation of transcription factors or epigenetic changes, which regulate gene expression in the hypertrophied heart [65]. To date several lncRNAs have been interrogated for their role in hypertrophic remodelling (Fig. 3).

2.2. lncRNAs in cardiac hypertrophy

The first paper describing a role for lncRNAs in cardiac hypertrophy was published in 2014 by Han et al. [66]. These authors identified a new antisense transcript of *myosin heavy chain 7* (*Myh7*) formed by alternative splicing, named *Myosin Heavy Chain Associated RNA Transcripts (MHRT)*. *MHRT* is cardiac specific and highly expressed in the mouse and human adult heart. It functions by antagonizing brahma-related gene 1 (Brg1), blocking its recognition site for genomic DNA, and thereby influencing gene regulation by chromatin remodelling. The *MHRT*-Brg1 feedback circuit appears to be crucial for heart function and potentially has a conserved role in humans. The human orthologue of *MHRT* also overlaps MYH7 on the opposite strand, which makes it an interesting lncRNA for further research. *MHRT* has already been suggested as a biomarker for predicting HF in humans [67].

More recently, the lncRNAs *cardiac hypertrophy-associated transcript* (*Chast*) and *cardiac-hypertrophy-associated epigenetic regulator* (*Chaer*) were identified [68,69]. Both are increased upon pressure overload-induced HF in mice and are conserved in humans. *Chast* overexpression induced cardiomyocyte hypertrophy *in vitro* and *in vivo*, whereas silencing of *Chast* attenuated cardiac remodelling after pressure overload. It was suggested that *Chast* functions by a cis-regulatory action on the gene located on the opposite strand: *pleckstrin homology domain-containing protein family M member 1*, an autophagy regulator [70]. However, the exact mechanism of action remains to be elucidated and the connection to cardiac hypertrophy is at the moment unclear. *Chaer*, on the other hand, functions through the direct interaction with the catalytic subunit of a protein, polycomb repressor complex 2 (PRC2), and influences the chromatin remodelling function of PRC2. PRC2 can bind to genomic loci and inhibit the methylation of histone H3 lysine 27. In this way, *Chaer* can affect epigenetic reprogramming of the expression of genes involved in cardiac hypertrophy. Therefore,

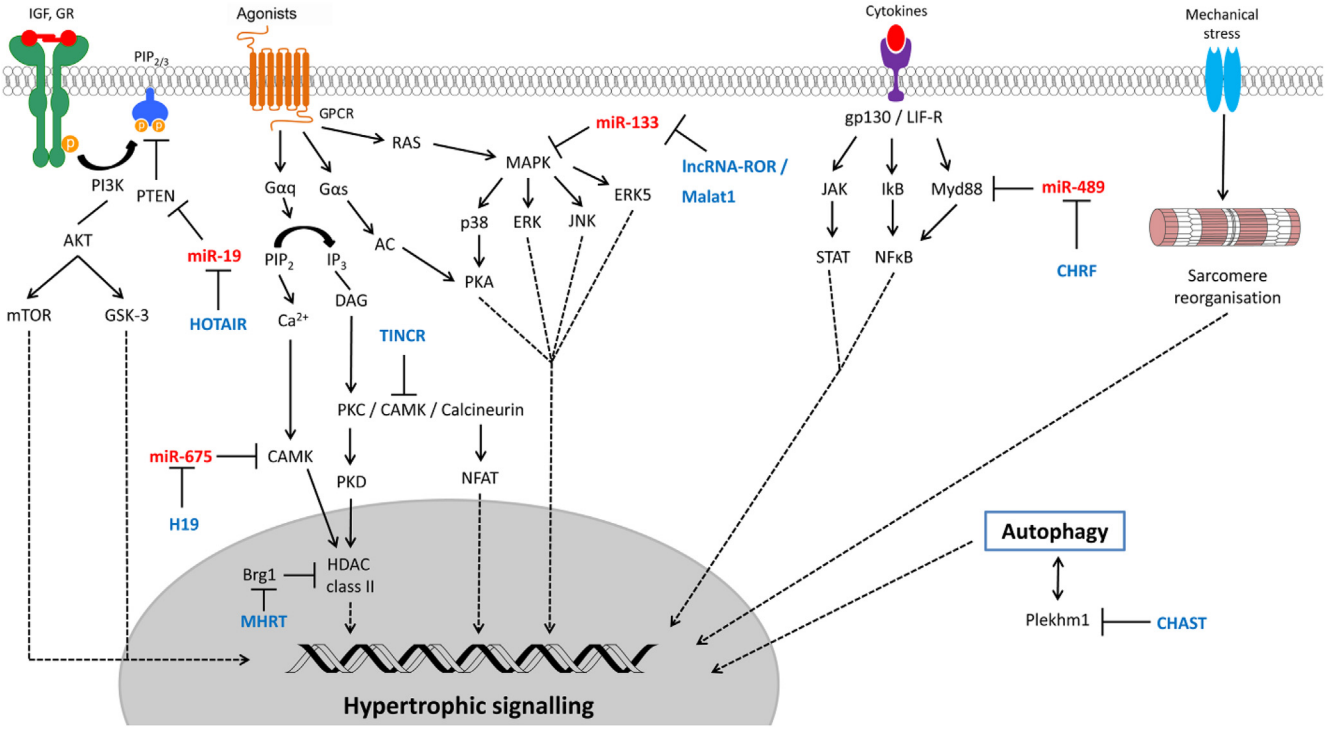

Fig. 3. lncRNAs affect hypertrophic signalling in cardiomyocytes. Mechanical or neurohormonal triggers can activate receptors on the cardiomyocyte cell membrane. Cardiomyocytes sense these signals, such as agonists (endothelin-1, angiotensin II), IGF-I, and cytokines, that activate intracellular signalling pathways. These pathways include MAPK, calcineurin-NFAT, PI3K-AKT, JAK/STAT, and chromatin remodelling by HDACs. Activation of these pathways initiates hypertrophic growth of the cardiomyocyte. LncRNAs regulate signalling at different levels, by either direct or indirect (possibly via microRNA silencing) inhibition. Abbreviations: Brg-1, brahma-related gene 1; CAMK, calmodulin-dependent protein kinase; ERK, extracellular-regulated kinases; GPCR, G-protein-coupled receptors; GR, growth factor; GSK-3, glycogen synthase kinase 3; HDACs, histone deacetylases; IGF, insulin-like growth factor; IκB, inhibitors κB; JAK, janus kinase; JNK, c-jun N-terminal protein kinases; LIF-R, leukemia inhibitory factor receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; Myd88, myeloid differentiation primary response 88; NFκB, nuclear factor-κB; NFAT, nuclear factor of activated T cells; PI3K, phosphatidylinositol 3-kinase; $PIP_{2/3}$, phosphorylating phosphatidylinositol-4, 5-bi/tri phosphate; Plekhm1, pleckstrin homology domain-containing family M member 1; PKA, protein kinase A; PKC, protein kinase C; PKD, protein kinase D; PTEN, phosphatase and tensin homolog; STAT, signal transducer and activator of transcription.

both *Chaer* and *Chast* play a key role in the development of cardiac hypertrophy and failure, though their mechanism of action differs significantly.

Another lncRNA that seems to play an important role in cardiac hypertrophy is *terminal differentiation-induced ncRNA* (*TINCR*). Forced expression of this lncRNA attenuated cardiac hypertrophy in mice, and decreased calmodulin-dependent protein kinase IIδ (CAMKIIδ) expression by directly targeting enhancer of zeste 2 (EZH2) [71]. EZH2 is a methyltransferase that plays a fundamental role in H3K27me3 modification and can bind to the CAMKIIδ promoter region to regulate its expression [72]. The lncRNA *TINCR* is annotated in human, and has been exclusively studied in cancer where it affects KLF2 mRNA stability and thereby cyclin-dependent kinases [73]. Nonetheless, lncRNA *TINCR* regulates cardiac hypertrophy in mice and might be an interesting therapeutic target.

Malat1 is a well-conserved lncRNA which is highly expressed in many tissues, including the heart. *Malat1* is involved in mRNA splicing and reduces revascularization capacity in ischaemia [42,74,75]. Surprisingly, knocking out *Malat1* in mice is not detrimental and they have a normal development [76–78]. In addition, pathological cardiac remodelling by transverse aortic constriction (TAC) is similar in *Malat1* knockout mice as in wildtype mice [79]. However, in these mice only the first two exons (including start codon) are knocked out, potentially leaving the possibility to produce the 3′-end transcript mascRNA (unpublished observations).

Taken together, emerging evidence indicates that multiple lncRNAs are implicated in the regulation of cardiac hypertrophy. The majority of the lncRNAs described above are working via a scaffold-based mechanism, in which they prevent targets from exerting their functions.

2.3. CeRNAs in cardiac hypertrophy

The ceRNA hypothesis proposed by Salmena et al. states that RNA transcripts (mRNA, pseudogenes, lncRNAs) communicate via miRNA response elements (MREs) [43]. In the conventional way of thinking, miRNAs regulate mRNA levels. This hypothesis, on the other hand, suggests that 1) RNAs can regulate specific miRNAs by binding them and reduce their availability and activity, and 2) RNAs can bind to mRNAs and block the binding site of miRNAs. It has already been demonstrated that the pseudogene *PTENP1* regulates protein levels of phosphatase and tensin homologue (PTEN) by binding to MREs of the mRNA of *PTEN*, hence preventing miRNA-mediated repression of *PTEN* expression [80].

Several recent studies provide evidence that some lncRNAs indeed act via miRNAs, thus supporting the ceRNA hypothesis. The lncRNA *cardiac hypertrophy related factor* (*CHRF*) is upregulated in cardiomyocyte hypertrophy where it scavenges miRNA-489 and thereby indirectly regulates the levels of the target gene *myeloid differentiation primary response gene 88* (*Myd88*) [81]. Previous studies had already shown that the Toll-like receptor 4-mediated, MyD88-dependent, nuclear factor-κB (NFκB) pathway is involved in cardiomyocyte hypertrophy [82]. Similar roles have been attributed to the lncRNA *myocardial infarction-associated transcript* (*MIAT*) and lncRNA *H19*, which act by sponging miRNA-150 and miRNA-675 respectively, affecting CAMKIIδ levels in cardiomyocytes [83,84]. CAMKIIδ-mediated HDAC inactivation has been well studied in cardiac hypertrophy and is a key modulator in the development of HF [85–87]. All these lncRNAs were investigated in the context of cardiac hypertrophy, but none of these studies elaborated on the underlying molecular mechanism.

Another central pathway in cardiac growth is the MAPK signalling pathway. Ligand binding to G-protein-coupled receptors, reactive oxygen species (ROS) and environmental stress, activate a signalling cascade of proteins that ultimately results in activation of the transcription factors, which regulate cardiac gene expression [61,63].

LncRNA *human large intergenic non-coding RNA ROR* (*lncRNA-ROR*) influences MAPK signalling by acting as a sponge for miRNA-133 [88]. miRNA-133 has been extensively studied in cardiac hypertrophy and has been implicated in targeting key regulators of cardiac disease including serum response factor (SRF), connective tissue growth factor, CDC42, and many others [89]. In addition, lncRNA *Malat1* has also been shown to act as a ceRNA by scavenging miRNA-133, and thereby affecting myocyte differentiation by SRF [90]. As well as MAPK signalling, PI3K-AKT signalling is very important in cardiac hypertrophy [62,64]. LncRNA *HOTAIR* may function as a sponge to modulate PTEN levels via miRNA-19, connecting another lncRNA with the miRNA-mRNA inhibiting concept [91]. miRNA-19 can inhibit PTEN expression, a protein which is directly linked to PI3K-AKT signalling. The collective findings suggest that several lncRNAs are important regulatory factors in cardiac hypertrophy through ceRNA activity. Still, the exact mode of action of these lncRNAs is unclear and needs to be further investigated.

2.4. Transcriptome analysis of lncRNAs in cardiac hypertrophy

In addition to the limited number of studies on the roles of known lncRNAs in cardiac hypertrophy (described above), several groups have performed transcriptome analyses of the hypertrophic and/or failing heart to identify (new) lncRNAs that could be relevant for the development of cardiac hypertrophy [92–96]. These studies include microarray analysis or RNA sequencing of human ischaemic heart failure tissue compared to embryonic mouse heart tissue [97], human iPSC-derived cardiomyocytes subjected to endothelin-1 [93], mouse hearts one and four weeks after TAC [92,95], rat hearts four weeks after TAC [98], and mouse hearts one week after β-adrenergic receptor activation by isoproterenol injection [94]. Interestingly, Matkovich et al. concluded that lncRNA expression responses upon TAC are surprisingly mild, with only 17 differentially expressed lncRNAs as compared to sham hearts [92]. In sharp contrast, one week of β-adrenergic receptor activation resulted in a tremendous change in cardiac lncRNA profiles, with over a 1000 lncRNAs up- and down-regulated as compared to saline injection [94]. Similar numbers of differential lncRNAs were identified in mouse hearts upon four weeks of TAC by Sun et al. [95]. These huge deviations in numbers of differentially expressed genes may not be biologically meaningful, given the diversity of (statistical) analyses used by these studies. Unfortunately, the poor annotation of lncRNAs makes it currently unfeasible to compare studies and to identify any potential overlap.

A further confounding factor is that transcriptome analysis of cardiac tissue includes transcripts from all the cell types in the heart, with cardiomyocytes outnumbered by non-cardiomyocytes at least 1:3 in the adult mammalian heart [99]. This makes it challenging to identify lncRNAs that are cell type-specific and are involved in cell type-specific processes, in particular those lncRNAs that are low expressed. To overcome this, fluorescence activated cell sorting or magnetic-activated sorting of cell type specific nuclei can be applied [100,101]. Both methods could be useful to identify cell type-specific lncRNAs. However, one should keep in mind that the process of isolating heart cells can provoke a stress reaction (for example using Langendorff method or during cardiac neonatal cell isolation), which might influence gene expression. When sorting solely cellular nuclei this can be widely prevented, since they originate from snap frozen tissue and are isolated using enzymatic inhibitors [102].

Few studies so far have then gone on to further characterise lncRNAs identified by transcriptome analyses. LncRNA *BC088254*

was identified upon TAC in rat hearts [98], and found to correlate with prohibitin 2 (PHB2) expression, a membrane-bound mitochondrial protein important in mitochondrial fission and apoptosis in cardiomyocytes [103]. It was suggested that lncRNA *BC088254*, via its effect on PHB2, plays an important role in the process of mitochondrial dynamics and function. However, exactly how these factors affect cardiac disease and specifically cardiac hypertrophy, remain elusive. In addition, *CARMEN*, identified by transcriptome analysis and upregulated in human HF, turns out to be a crucial regulator for cardiac cell differentiation and homeostasis, and acts as a super enhancer-associated lncRNA [97]. This class of enhancers epigenetically regulates key elements of the transcription machinery during (disease-associated) cellular processes. During cardiac differentiation the expression pattern of *Braveheart* (*Bvht*), a lncRNA originally identified in mouse [104], was comparable to that of *CARMEN*. As such, it will be interesting to explore the role of both transcripts in the development of HF.

In summary, these studies revealed that lncRNAs are of significance during the development of cardiac hypertrophy and failure. If the differential expressed lncRNAs upon cardiac hypertrophy and remodelling indeed outnumber the 1000, as suggested by some studies described above, a huge number of new lncRNAs remains to be explored. It is difficult to establish whether there is overlap in newly identified lncRNAs between studies, mainly because of the use of different lncRNA annotations. Above all, the exact mechanism of action of the lncRNAs putatively implicated in cardiac disease still remains to be elucidated.

3. LncRNAs in cardiac fibrosis

3.1. Cardiac fibrotic signalling

Cardiac remodelling is a pathological process in which, besides cardiomyocyte hypertrophy, cardiac fibroblasts (CFs) proliferate, differentiate into myofibroblasts, and produce extra cellular matrix (ECM) proteins. Excessive ECM production can lead to increased ventricular stiffness and impaired contractility, which can progress into HF [105]. CFs regulate ECM homeostasis, which provides a structural scaffold for cardiomyocytes and promotes efficient electric conduction throughout the myocardium [106]. Myocardial injury can cause a series of cellular responses: activation of the inflammatory response, proliferation of CFs, and thickening of the myocardium. These processes are partly regulated by CFs. CFs can produce pro-inflammatory cytokines and pro-fibrotic factors, which lead to an increase in proliferation and ECM production (fibrosis). There are two types of fibrosis: interstitial fibrosis and perivascular fibrosis. In mouse pressure overload models, the initial response of the heart to the increased pressure is fibroblast hyperproliferation inciting interstitial fibrosis, which over time will be followed by replacement fibrosis [107]. In ischaemic/reperfusion models or MI models, the acute inflammatory response causes excessive cardiomyocyte cell death, which is directly filled up by replacement fibrosis [108].

Currently, transforming growth factor (TGF)-β is believed to be the most important pro-fibrotic factor and TGF-β receptor-mediated signalling is thought to play a major role in cardiac pathological fibrosis [109]. Both the canonical and non-canonical TGF-β1 signalling pathways lead to transcriptional regulation of pro-fibrotic genes [110]. In addition, the renin-angiotensin system, adrenergic signalling, RhoA - myocardin-related transcription factor - SRF signalling, growth factors, integrins and many additional pathways, have been described to influence the fibrotic response in CFs [105]. Which lncRNAs are involved, and how they affect these pathways, is still unclear. However, several lncRNAs were identified in ischaemic heart disease and shown to have a role in fibrosis [44,111–114]. These studies are described in the next paragraph.

3.2. LncRNAs in ischaemic heart disease

Acute MI (AMI) can occur when an atherosclerotic plaque ruptures, which results in an intraluminal thrombus in one or more of the coronary arteries. This causes extreme ischaemia in the surrounding cardiac tissue, ultimately leading to myocardial cell death. Once the cardiac tissue is dead, it will be cleaned up by surrounding and invading cells, and CFs will replace the necrotic tissue with ECM proteins, primarily collagen. Several lncRNAs have been investigated specifically in the setting of MI and have been shown to play an important role in the post-MI remodelling process.

MIAT was discussed earlier in relation to cardiac hypertrophy. *MIAT* also plays a role in the cardiac responses upon MI, including fibrosis [115]. *MIAT* is upregulated in a mouse model of MI and knocking it down improves cardiac function. In addition, lowering *MIAT* expression inhibits collagen production and CF proliferation, which results in less interstitial fibrosis after MI. These authors propose a mechanism in which *MIAT* functions as a sponge for miRNA-24 in CFs.

Piccoli et al. were the first to study the role of CF-enriched lncRNAs in the development of cardiac fibrosis [116]. LncRNA *maternally expressed gene 3* (*Meg3*) was downregulated in CFs during late cardiac remodelling, where it modulates the expression of matrix metalloproteinase-2 (Mmp-2) in a p53-dependent manner. *Meg3* blocks the recognition site for p53 on the Mmp-2 promoter as shown by immunoprecipitation. Depleting *Meg3* levels *in vivo* after TAC attenuated cardiac fibrosis and improved diastolic function. Previously it has been shown that *Meg3* recruits components of PRC2 to specific genomic locations, acting as a guide lncRNA [117,118].

Recently, is was demonstrated that another lncRNA, *Wisp2 super-enhancer-associated RNA* (*Wisper*), has a major effect on the development of cardiac fibrosis [119]. *Wisper* was found to influence CF proliferation, migration and survival, and in this way controls CF-specific gene programs. Depleting *Wisper* levels *in vivo* attenuated MI-induced fibrosis and improved cardiac function. More importantly, reducing the levels of *Wisper* two days post-MI improved cardiac function, thereby demonstrating therapeutic potential of this lncRNA.

Several other lncRNAs have been implicated in MI, including *myocardial infarction-associated transcript 2* (*MIRT2*) [120], *NONRATT021972* [121,122], and *MHRT* [123]. In addition, transcriptome analysis of heart tissue identified novel lncRNAs that are possibly involved in processes underlying cardiac ischaemic injury in mouse and human [124,125]. However, the precise role of these lncRNAs in cardiac fibrosis and ischaemic heart disease remains elusive.

LncRNAs are also under consideration as potential biomarkers of HF or specific underlying pathophysiological processes including fibrosis. Vausort et al. showed that lncRNAs might serve as biomarkers for AMI and possibly help predicting outcome. Levels of lncRNAs *ANRIL*, *KCNQ1OT1*, *MIAT* and *Malat1* in the blood of AMI patients can predict left ventricular dysfunction [126]. Another study showed that lncRNA *HOTAIR* is decreased in serum of AMI patients compared to healthy controls. *HOTAIR* has a possible cardioprotective function by regulating apoptosis via miRNA-1 [127]. Still, lncRNAs serving as biomarkers have a long way to go before, if ever, becoming clinically applicable, in particular since their circulating levels are extremely low.

3.3. LncRNAs in cardiac cell death

Apoptosis and necrosis are the two main mechanisms by which cell death occurs. Cell death is an important characteristic of

ischaemic heart disease. During ischaemic stress in the heart, there is a lack of oxygen delivery to the heart, which causes cardiomyocyte cell death. Multiple studies focussed on the role of lncRNAs in cell death, and how they affect ischaemic injury of the myocardium [128–133].

Although autophagy was initially thought to be a cell survival process, it is now being linked to both apoptosis and necrosis, serving as both pro-survival and pro-cell death regulator [134]. Through autophagy, cytoplasmic components get recycled. In the heart, autophagy is altered upon ischaemic stress, but also in cardiac hypertrophy [135,136]. Autophagy is controlled by *autophagy related genes* (*ATG*), many of which are involved in autophagosome formation [137]. A newly identified lncRNA, named *autophagy promoting factor* (*APF*), regulates one of the *ATG* genes. *APF* acts as a ceRNA and regulates *ATG7* expression, and subsequently cardiac autophagy via miRNA-188. In this way, *APF* is able to regulate autophagy and cell death in the heart after MI [138]. It should be noted, however, that *APF* is poorly conserved across species, which makes translation to the human situation difficult. Furthermore, *APF* is expressed at very low levels, problematizing its potential as biomarker. A new lncRNA which is associated with cell death, is *β-secretase-1 antisense transcript* (*BACE1-AS*). *BACE1-AS* was upregulated in HF patients with ischaemic cardiomyopathy compared to controls [139]. *BACE1-AS* induces β-secretase-1 (BACE1) expression, as well as, β-amyloid peptide accumulation. Since increased levels of *BACE1-AS* and β-amyloid induce toxicity in endothelial cells and cardiomyocytes, the *BACE1-AS*/BACE1/β-amyloid pathway was considered to have detrimental effects on the cardiovascular system.

Besides its roles in chromatin remodelling during cardiac hypertrophy, lncRNA *MHRT* is implicated in AMI, and plays a role in H_2O_2-induced cardiomyocyte apoptosis [123]. H_2O_2 exposure serves as an *in vitro* model to study apoptosis, and is a way to investigate this pathway for the purpose of ischaemic disease. Several lncRNAs interfere with this pathway and contribute to the current knowledge about ischaemia/reperfusion injury. *KCNQ1OT1* silencing prevents increased expression of inflammatory factors, apoptosis-related proteins, and p38 MAPK/NF-kB pathway-related proteins, upon ischaemia-reperfusion injury in cardiac muscle cells [140]. In addition, *Urothelial carcinoma-associated 1* (*UCA1*) is a lncRNA which negatively correlates with p27, a known tumour suppressor gene involved in caspase 3 activity and cellular apoptosis [141]. The lncRNA *necrosis-related factor* (*NRF*) acts on a different pathway leading to cell death, as the name suggests. Necrosis in cardiomyocytes is induced by activating a necrosis-inducing complex, consisting of serine/threonine-protein kinase 1 (RIPK1) and 3 (RIPK3). *NRF* acts as an endogenous sponge, thereby repressing the action of miRNA-873, and regulating the RIPK1/RIPK3-necrosis pathway [142].

Although limited data is available, most of the lncRNAs found to be involved in cardiac fibrosis up to now, act as ceRNA, and affect cardiac fibrosis and apoptosis indirectly through their interaction with miRNAs. Some of them have potential to act as therapeutic targets for treating cardiac disease.

4. LncRNAs in cardiac inflammation

One of the first responses of the body to injury is inflammation. In addition, chronic low-grade inflammation is a hallmark of metabolic syndrome and its associated conditions, including hypertension, diabetes and obesity, which are important risk factors for HF development. Inflammation, whether as an acute response to injury or the result of a more chronic systemic disease state, is one of the key processes involved in the development of HF. Cardiac inflammation has been mostly studied in myocarditis, sepsis, ischaemia and reperfusion, and allograft rejection [143]. Invading pathogens can cause acute inflammation in the heart (myocarditis) and sepsis with possible cardiac death. The term “septic cardiomyopathy” defines an acute and reversible status with left ventricular systolic dysfunction [144]. During a septic shock, endotoxins like lipopolysaccharide (LPS) activate the production of pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), and interleukins. *HOTAIR*, a well-studied lncRNA, seems to play a role in the heart during sepsis. *HOTAIR* silencing can improve cardiac function during sepsis in mice, and is proposed to exert its effect via inhibition of NFκB and TNF-α [145]. In addition, LPS-induced sepsis increased the expression of *Malat1* in the heart. Increased *Malat1* levels in LPS-stimulated cardiomyocytes control the expression of TNF-α, partly via serum amyloid antigen 3 [146]. In addition, *myocardial infarction-associated transcript 1* (*MIRT1*) was shown to have a role in cardiomyocyte apoptosis and inflammatory cell infiltration in the heart. Suppressing *MIRT1* levels attenuated injury in an AMI mouse model, partly by affecting the NFκB pathway [147]. Altogether, *HOTAIR*, *Malat1,* and *MIRT1,* seem to play a role in the development and progression of inflammation, though their mode of action remains largely elusive.

Cardiac inflammation also occurs during allograft rejection after heart transplantation. The innate and adaptive immune responses play an important role in these patients, and lncRNAs have been studied to regulate the immune response-related genes in B and T cells [148,149]. Gu et al. identified differentially expressed lncRNAs after allograft rejection in an allogeneic and syngeneic mouse heart transplantation model, and generated a lncRNA-mRNA coexpression network. They found two lncRNAs, *ncRNA-A930015D03Rik* and *mouselincRNA1055*, that correlated with the Th1 response after transplantation. In differentiated Th1 cells *in vitro*, they show that knockdown of these two lncRNAs can regulate the immune response by suppressing IL-12Rβ1, Interferon-γ, and TNF-α expression. In addition, detection of these lncRNAs in peripheral blood lymphocytes indicates their potential as possible biomarkers of cardiac inflammation [150].

These studies show the role of lncRNAs in cardiac inflammation with the main focus on sepsis and the immune response to allografts. Nonetheless, cardiac inflammation plays a much broader role in the transition towards HF [151]. Therefore, future studies are warranted to identify lncRNAs playing central roles in cardiac inflammation, leading to HF [152].

5. LncRNAs in vascular disease

Chronic hypertension, atherosclerosis, and peripheral vascular disease, are important vascular risk factors for HF development. They can cause vascular remodelling, a process that leads to vascular dysfunction and is controlled by many different factors, including inflammatory cytokines, hemodynamic stimuli, and proliferation and migration of endothelial cells, pericytes, fibroblasts, and vascular smooth muscle cells [153,154].

5.1. Endothelial cell functions controlled by lncRNAs

Up to now, several lncRNAs have been identified that play a role in endothelial cells, all regulating angiogenic function. Fiedler et al. identified two intergenic lncRNAs, *LINC00323* and *MIR503HG*, to be upregulated in endothelial cells during hypoxia [155]. Endothelial loss of these hypoxia-driven lncRNAs impaired cell-cycle control and inhibited capillary formation. Still, more in-depth mechanistic studies are needed to fully understand the mode of action of these lncRNAs. Moreover, these lncRNAs are poorly conserved, challenging the *in vivo* study of these lncRNAs in vascular disease in different species models. The third lncRNA linked to endothelial cell

function, *MANTIS*, has been shown to interact with Brg1 in the nucleus, regulating the expression of endothelial genes and facilitating angiogenic sprouting [156]. *MANTIS* levels are under the control of the histone demethylase JARID1B, and act as a scaffolding lncRNA within a chromatin-remodelling complex, mediating and directing endothelial gene transcription in order to control endothelial cell function.

5.2. Perivascular cell functions controlled by lncRNAs

Next to endothelial cells, perivascular cells, including smooth muscle cells and pericytes, also play pivotal roles in vascular remodelling in response to hypoxia or other hemodynamic stimuli. Silencing of the hypoxia-induced lncRNA *Malat1* caused proliferation and migration of human pulmonary artery smooth muscle cells. Silencing of *Malat1* in a mouse model of hypoxia-induced pulmonary hypertension attenuated cardiac hypertrophy, this effect could not be linked to the vascular smooth muscle cell function of *Malat1* [157]. In an earlier study, *Malat1* knockout mice showed no differences as compared to wildtype littermates in pressure overload-induced cardiac left ventricular hypertrophy [79]. Taken together, the vascular function of *Malat1* requires further studying, in particular, in *in vivo* pathophysiological settings.

One of the first lncRNAs with a potential role in the vasculature was *lnc-Ang362*. This lncRNA was upregulated in response to AngII treatment in rat vascular smooth muscle cells, and knocking it down reduced cell proliferation [158]. Unfortunately, no further pathophysiological insights into the potential role of this *lnc-Ang362* have emerged since then. It is noteworthy, that *lnc-Ang362* may be the host transcript for miRNA-221 and -222. Conceivably, the cellular function of *lnc-Ang362* may be attributed to these miRNAs, which are both important in cell proliferation [159,160].

Only one paper so far has reported on a role for a lncRNA in pericyte function. Pericytes surround endothelial cells in the smaller vessels and capillaries, where they control the endothelial permeability and angiogenesis. *Hypoxia-Induced Endoplasmic Reticulum Stress Regulating* lncRNA (*HypERlnc*) was induced by hypoxia in human primary pericytes, and modulates pericyte differentiation, proliferation, and endothelial permeability [161]. Loss of *HypERlnc* resulted in enhanced endoplasmic reticulum (ER) stress in pericytes. Interestingly, ER stress has been proposed to play a major role in cardiovascular pathology and ageing. In addition, these authors observed downregulation of *HypERlnc* levels in human failing hearts. The exact molecular role of *HypERlnc* in ER stress remains to be identified, although the effects on pericytes suggest a role in vascular remodelling. Also, the exact role of this lncRNA in cardiovascular pathophysiology remains to be addressed, a task that is complicated, as for many lncRNAs, by the poor sequence conservation of *HypERlnc*.

6. LncRNAs in ageing

Ageing is a dynamic process affecting all living beings. The increasing lifespan of humans has led to a parallel increase in the incidence of CVD. By 2020, over 20 million people will die annually due to CVD. Many physiological processes are involved in ageing; here we will focus on their effect on the heart and vessels. Cardiac ageing increases the incidence of atherosclerosis, hypertension, MI, and stroke [162–165]. Characteristics of cardiac ageing include pathological remodelling of the myocardium (hypertrophy) with decreased diastolic function. In the vasculature, increased vessel stiffness and impaired endothelial function, are features of ageing [166]. Our previous paragraphs describe lncRNAs involved in most of the processes involved in ageing (Table 1). Hypertrophy, fibrosis, inflammation, and vascular diseases, are processes co-presented with increased age, either individually or collectively.

Up to now, lncRNAs haven't been investigated specifically in cardiac ageing. However, a number of lncRNAs have been identified to be important in processes involved in ageing, in general. Cellular senescence is one of the key processes of ageing. Replicative senescence, in which cell proliferation is terminally arrested due to progressive telomere erosion, or other DNA-damaging stressors (ultraviolet radiation, ROS, stress), can lead to early senescence which later turns into full senescence [167]. Cardiomyocyte senescence is associated with multiple cellular processes, for example, production of ROS by mitochondria. Enhanced ROS production compromises normal cellular function and promotes organ dysfunction, which leads to a decreased lifespan in animals. In addition, the anti-apoptotic and anti-oxidative stress response in cardiomyocytes contributes to senescence and cardiac ageing [168].

While cardiomyocytes are terminally differentiated and largely lack proliferating capacity, telomere shortening in cardiomyocytes is pronounced in HF patients [169]. Telomere erosion, as a result of telomerase knockout, causes telomere shortening upon each cell cycle and results in senescent cells. The noncoding *telomeric repeat-containing RNA*, *TERRA*, can base-pair with the RNA template of telomerase and can also bind to the telomerase reverse transcriptase polypeptide to inhibit telomerase activity [170,171]. As a result, cells expressing increased levels of *TERRA* are pushed into early senescence. Interestingly, unlike most lncRNAs the structure and function of *TERRA* is conserved among eukaryotes, rendering *TERRA*-mediated regulation of telomerase a promising therapeutic strategy against cancer and age-associated diseases.

Abdelmohsen et al. used RNA sequencing to identify lncRNAs involved in cellular senescence by comparing expressed transcripts in proliferating cells and terminally arrested cells [172]. Interestingly, *Malat1*, one of the most widely-studied lncRNAs, was downregulated in senescent cells. This lncRNA has already been shown to be involved in cell cycle arrest; knockdown of *Malat1* blocks the progression of the cell cycle at the G1/S phase, resulting in more senescence-like cells [173,174].

Age is one of the major risk factors of HF, and studying the role of lncRNAs in cardiac ageing may contribute to a better understanding of the molecular processes that make up the aged and failure-prone heart.

7. Therapeutic potential of lncRNAs

Current HF therapy is based on (a combination of) renin-angiotensin-aldosterone system blockers and β-blockers. Although these medical treatments are quite successful, the mortality rate of HF patients within 2,5 years is still over 40% [175]. Accordingly, there is a need for alternative therapies. NcRNAs provide an interesting class of molecules for therapeutic use. As outlined in this review, they are involved in a number of crucial processes related to the initiation or progression of disease. In addition, ncRNAs can be targeted by sequence-specific antisense oligonucleotides (ASOs) or small interfering RNAs (siRNAs). Both ASOs and siRNAs act via the Watson-Crick base pairing principle, but differ in their structure [176]. One of the most widely used ASOs inhibit lncRNAs are GapmeRs, single stranded antisense oligonucleotides that bind to their target RNA by specific recognition of a complementary sequence within the RNA [177,178]. The resulting double-stranded DNA:RNA heteroduplex causes the activation of RNAse H, which mediates cleavage of the duplex and subsequent degradation of the full-length lncRNA [177,179]. On the other hand, siRNAs consist of two RNA strands, an antisense (or guide) strand and a sense (or passenger) strand, which form a duplex of 19–25 bp in length. This RNA duplex associates with the RNA-induced silencing complex (RISC), the passenger strand is lost, and the

Table 1
lncRNAs associated with the cellular processes involved in the development of CVD.

lncRNA	Risk factor CVD	Expression	Species	Target	Reference
MHRT	Hypertrophy	↓ upon TAC	Mouse	Brg1	[62]
	Fibrosis	↑ in AMI	Human	?	[118]
Chast	Hypertrophy	↑ upon TAC	Mouse	Plekhm1	[64]
		↑ in AOS	Human		
Chaer	Hypertrophy	↓ upon TAC	Mouse	PRC2	[65]
TINCR	Hypertrophy	↓ upon TAC	Mouse	EZH2	[67]
CHRF	Hypertrophy	↑ upon AngII	Mouse	miR-489	[77]
MIAT	Hypertrophy	↑ upon AngII	Mouse	miR-150	[79]
	Fibrosis	↑ upon MI	Mouse	miR-24	[110]
H19	Hypertrophy	↑ upon TAC	Mouse	miR-675	[80]
lncRNA-ROR	Hypertrophy	↑ upon TAC	Mouse	miR-133	[84]
HOTAIR	Hypertrophy	↓ upon TAC	Mouse	miR-19	[87]
	Fibrosis	↓ in AMI	Human	miR-1	[122]
	Inflammation	↑ upon sepsis	Mouse	?	[140]
CARMEN	Hypertrophy	↑ upon MI	Mouse Human	SUZ12/EZH2	[93]
		↑ in DCM/AOS			
Meg3	Fibrosis	↓ upon TAC	Mouse	Mmp-2	[111]
Wisper	Fibrosis	↑ upon MI	Mouse	TIAR	[114]
		↑ in AOS	Human		
MIRT1	Fibrosis	↑ upon MI	Mouse	?	[142]
APF	Fibrosis	↑ upon I/R	Mouse	miR-188	[133]
BACE1-AS	Fibrosis	↑ in ischaemic HF	Human	BACE1/β-amyloid	[134]
		↑ upon MI	Mouse		
Malat1	Inflammation	↑ upon sepsis	Mouse	SAA3	[141]
HypERlnc	Vascular disease	↓ in HF	Human	?	[156]
Lnc-Ang362	Vascular disease	↑ upon AngII	Rat	?	[153]

Abbreviations: TAC, transverse aortic constriction; AMI, acute myocardial infarction; AOS, aortic stenosis; AngII, angiotensin II; MI, myocardial infarction; DCM, dilated cardiomyopathy; I/R, ischaemia/reperfusion; HF, heart failure.

guide strand cooperates with RISC to bind complementary RNA. The RISC complex mediates cleavage and degradation of the target RNA [180]. GapmeRs and siRNAs are examples of ASOs that are used to study the effect of lncRNAs *in vitro* and *in vivo*. The application of GapmeRs and siRNAs to knockdown lncRNA expression was already successful in various studies, showing their effect in cells and in animal models [68,75,181–184]. Furthermore, the first clinical trial has been launched using siRNAs against a specific lncRNA to modulate the Notch pathway and thereby regulatory B cell function, in patients with thymoma and autoimmune diseases (NCT02948855; Clinical trial database from US National Library of Medicine).

In addition to the possible therapeutic potential to target lncRNAs, a number of clinical trials are ongoing and are investigating the application of lncRNAs as biomarkers (NCT02304471; NCT03268135; NCT03152630; NCT02602808; NCT03000764; NCT03299335; NCT03279770; NCT03225183; NCT03076580). Interestingly, four out of these nine studies are being performed in patients with CVD, including heart failure, aortic stenosis, and atherosclerotic vascular disease (NCT03268135; NCT03279770; NCT03225183; NCT03076580; Clinical trial database from US National Library of Medicine).

The prospect of lncRNAs as biomarkers is moving forward [185–188], however many hurdles still have to be overcome. In general, lncRNA levels in the circulation are very low, making their accurate and reproducible measurement cumbersome. An option would be to focus on expression levels in peripheral blood cells, such as monocytes and platelets. RNA extraction of specific cell types can be analysed using RNA sequencing or microarray analysis. This approach has already been applied to CVD patients in a couple of studies [126,189].

Some hurdles will need to be overcome before lncRNAs become feasible therapeutic targets. Currently, technical challenges lie in the use of tools to overexpress or knockdown lncRNAs and/or their targets. Preclinical studies show great potential for some lncRNAs, but poor conservation is still an issue. Gaining knowledge about how lncRNAs act, and in which cellular processes they are involved, will help to identify therapeutic candidates. Nevertheless, human-specific lncRNAs and lncRNAs that are conserved have potential for future treatments of human disease. The GENCODE Consortium executed a great deal of experiments to investigate their potential and to map lncRNAs expressed in humans [99,190]. With close to 10,000 lncRNAs estimated to be transcribed from the human genome, the majority of which remain to be investigated. With the goal of finding their biological role, and to uncover their therapeutic potential.

8. Conclusion

Although many lncRNAs have been identified (and annotated), the understanding of their biological roles is in its infancy. Nonetheless, emerging evidence indicates that several lncRNAs play a major role in the development and progression of CVD. Functional studies targeting lncRNAs have been shown to affect cardiac function and outcome in preclinical models of fibrosis, cardiac hypertrophy, and sepsis. Future studies should focus on translating these findings to the human situation, and investigate their therapeutic potential for diagnosing or treating HF.

Conflicts of interest

The authors declare that they have no conflict of interest concerning this manuscript.

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