Post-transcriptional Regulation by Proteins and Non-coding RNAs

13

Amelia E. Aranega and Diego Franco

Contents

Abstract

Posttranscriptional regulation comprises those mechanisms occurring after the initial copy of the DNA sequence is transcribed into an intermediate RNA molecule (i.e., messenger RNA) until such a molecule is used as a template to generate a protein. A subset of these posttranscriptional regulatory mechanisms essentially are destined to process the immature mRNA toward its mature form, conferring the adequate mRNA stability, providing the means for pertinent introns excision, and controlling mRNA turnover rate and quality control check. An additional layer of complexity is added in certain cases, since discrete nucleotide modifications in the mature RNA molecule are added by RNA editing, a process that provides large mature mRNA diversity. Moreover, a number of

A.E. Aranega • D. Franco (✉)
Cardiovascular Research Group, Department of Experimental Biology, University of Jaén, Jaén, Spain
e-mail: dfranco@ujaen.es

S. Rickert-Sperling et al. (eds.), *Congenital Heart Diseases: The Broken Heart: Clinical Features, Human Genetics and Molecular Pathways,*
DOI 10.1007/978-3-7091-1883-2_13

posttranscriptional regulatory mechanisms occur in a cell- and tissue-specific manner, such as alternative splicing and non-coding RNA-mediated regulation. In this chapter we will briefly summarize current state-of-the-art knowledge of general posttranscriptional mechanisms, while major emphases will be devoted to those tissue-specific posttranscriptional modifications that impact on cardiac development and congenital heart disease.

13.1 Introduction

Posttranscriptional regulation comprises those mechanisms occurring after the initial copy of the DNA sequence is transcribed into an intermediate RNA molecule (i.e., messenger RNA) until such a molecule is used as a template to generate a protein. Posttranscriptional regulation is mainly mediated by distinct RNA-binding proteins (RBPs). RBPs are key components in RNA metabolism, regulating the temporal, spatial, and functional dynamics of RNAs. RBPs form dynamic interactions with coding, untranslated, and non-protein-coding RNAs in functional units called ribonucleoprotein (RNP) complexes [1, 2]. This enables the RBPs within RNP complexes to remain stably bound to the RNA throughout its journey from synthesis to degradation or to associate with the RNAs in a temporally and spatially specific manner. RNA molecules are constantly accompanied by RBPs, which are intimately involved in every step of RNA biology, including transcription, editing, splicing, transport and localization, stability, and translation. Altering the expression of RBPs has profound implications for cellular physiology, affecting RNA processes from pre-mRNA splicing to protein translation [1, 3]. RBPs therefore have opportunities to shape gene expression at multiple levels. This capacity is particularly important during development, when dynamic chemical and physical changes give rise to complex organs and tissues [2].

Modification of the nascent mRNA is a general mechanism that occurs in all cells within an organism. A subset of these posttranscriptional regulatory mechanisms essentially are destined to process the immature mRNA toward its mature form, conferring the adequate mRNA stability including modifications at the 5′ and 3′ ends (5′ capping and 3′ polyadenylation) as well as excision of pertinent introns by pre-mRNA splicing. mRNA turnover rate and quality control checking are performed by the nonsense-mediated decay (NMD) surveillance pathway. An additional layer of complexity is added in certain cases, since discrete nucleotide modifications in the mature RNA molecule are added by RNA editing, a process that provides large mature mRNA diversity. Given the fact that these posttranscriptional modifications would affect all RNA molecules, there are a very limited number of cases in which a discrete tissue layer or an organ, such as the heart, is affected since impairment impacts at the level of the organism. On the other hand, a number of posttranscriptional regulatory mechanisms occur in a cell- and tissue-specific manner, such as alternative splicing and non-coding RNA-mediated regulation. Alternative splicing is a major driver of mRNA diversity and consequently protein

diversity, affecting almost all genes within an organism. The use of alternative promoters or the generation of alternative mRNA species from a single gene locus has been reported widely in almost every biological context, providing extensive mRNA, and thus protein, diversity. In recent years a novel layer of regulation has been identified mediated by non-coding RNAs. Currently, short and long non-coding RNAs have been implicated modulating RNA expression at distinct biological levels, acting both as cis- and trans-acting factors. Importantly, tissue-specific expression of these short and long non-coding RNAs has been widely reported. In this chapter we will briefly summarize current state-of-the-art knowledge of general posttranscriptional mechanisms, while major emphases will be devoted to those tissue-specific posttranscriptional modifications that impact on cardiac development and congenital heart disease. While these processes are presented in the following subheadings as discrete events, it is important to highlight the intricate interrelationship between different posttranscriptional regulatory mechanisms.

13.2 mRNA Maturation: Generating Stability and Quality Control

The maturation of mRNA transcripts, from the time they are transcribed in the nucleus until they are exported into the cytoplasm, is accompanied by a series of general structural modifications (Fig. 13.1). A large number of RNA-binding proteins interact with the nascent transcript leading to the addition of modifications at the 5′ and 3′ ends as well along the coding sequence to basically stabilize the transcript and promote splicing whenever required [1, 2]. If impaired processing occurs, the NMD surveillance system is rapidly activated. In particular cases, editing of the nascent RNA transcript also occurs. Over the last years, we have gained much knowledge about the basic regulatory mechanisms orchestrating these events in eukaryotic cells, particularly in *Saccharomyces cerevisiae* and *Saccharomyces pombe*, while our understanding in metazoan cells has lagged behind.

13.2.1 5′ End Capping

Eukaryotic mRNAs are modified by the addition of a 7-methylguanosine "cap" to the first transcribed nucleotide in the nucleus (Fig. 13.1). This modification is necessary for efficient gene expression and cell viability from yeast to humans. The 7-methylguanosine cap is required for transcription elongation, splicing, translation, and general mRNA stability. On the other hand, the 5′ cap seems to be required for polyadenylation and nuclear export of mRNA in *S. cerevisiae* [4], but not in metazoan cells [5, 6]. Several factors have been reported to regulate mRNA cap methylation in yeast [7]. Triphosphatases such as Cet1p and Pct1 direct the hydrolyzation of RNA 5′ triphosphate to a diphosphate-RNA. Guanylyltransferases, such as Ceg1p and Pch1, catalyze the addition of CMP to the diphosphate-RNA to produce the guanosine cap [8], while the methylation of the guanosine cap is mediated

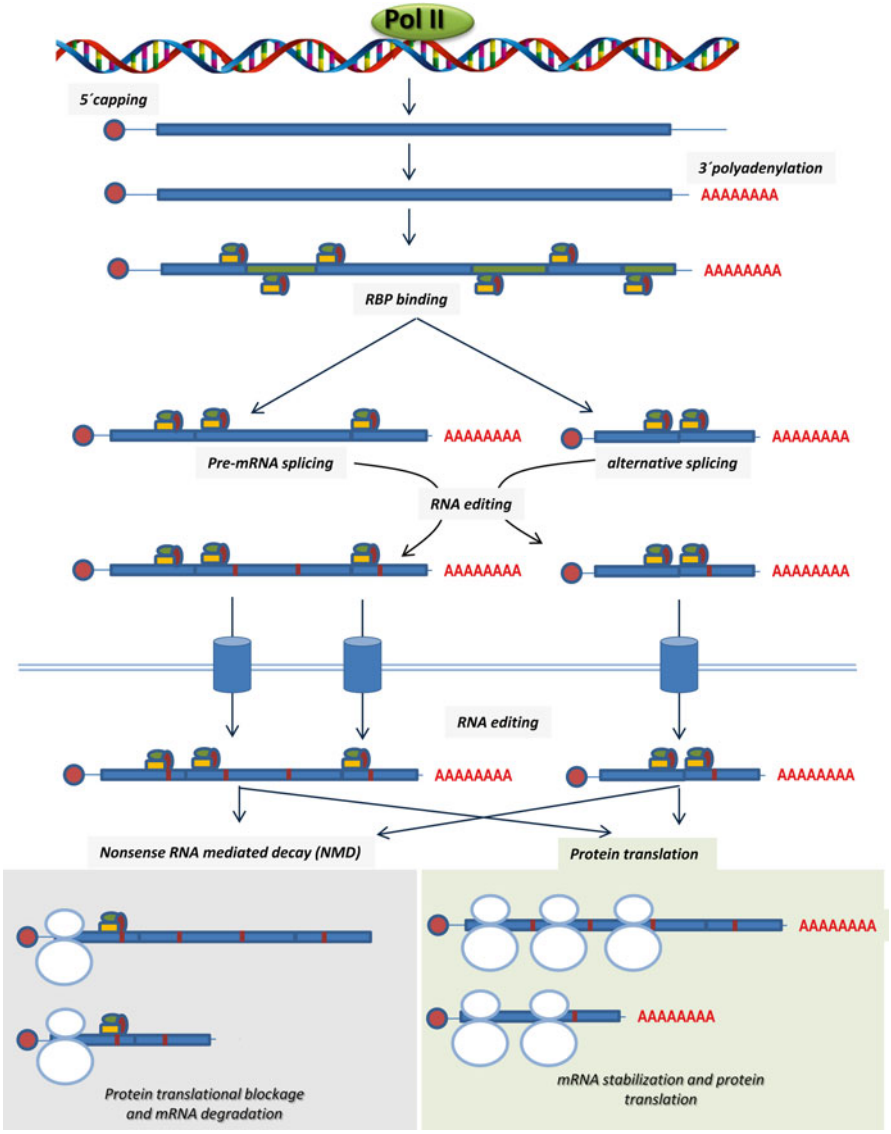

Fig. 13.1 Graphical representation of the distinct posttranscriptional regulatory mechanisms operating during the transcription, splicing, editing, quality control checking, and maturation of mRNA transcripts

by Abd1 and Pcm1. In mammals, the triphosphate and guanylyltransferase activities are found within the same peptide [9, 10] the capping enzyme of RNA guanylyltransferase and 5′ triphosphatase (RNGTT), while the RNA methyltransferase (RNMT) is encoded by a distinct protein [9–13]. Interestingly, guanylyltransferase

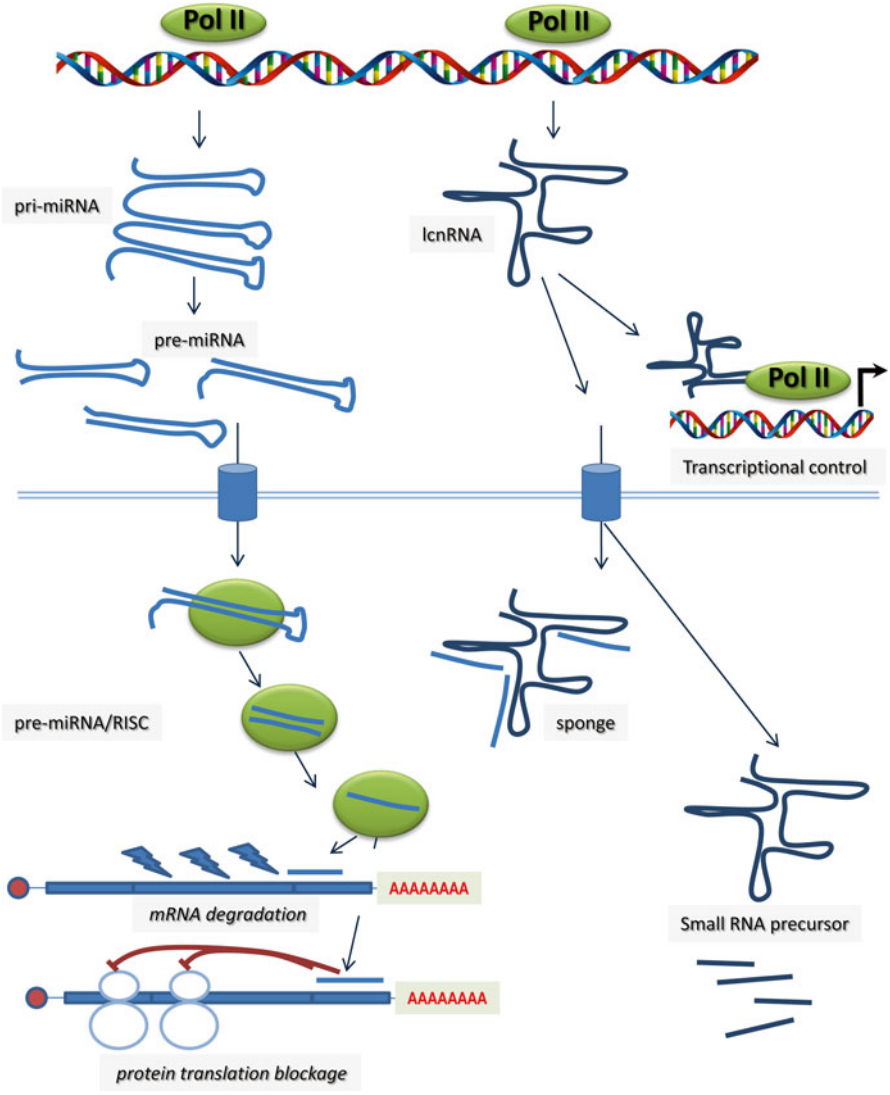

Fig. 13.2 Graphical representation of the microRNAs and long non-coding RNAs (lcnRNA) biosynthetic pathway and their functional roles during transcriptional and posttranscriptional regulation. microRNAs can elicit mRNA degradation and/or protein translation blockage. lncRNAs have been reported to actively contribute to transcriptional regulation and serve as sequestering small RNA system (sponge) or as template to generate smaller RNA molecules with, to date, poorly characterized functions

and methyltransferase are highly conserved in structure and function from yeast to humans, yet triphosphatases are widely divergent.

mRNA capping and cap methylation occur "co-transcriptionally," that is to say, the cap methyltransferase is recruited to RNA polymerase II as the RNA is

being transcribed, providing thus the means to promote transcription elongation [7]. Pre-RNA splicing is dependent on the 5′ cap since the splicing reaction has been demonstrated to be inhibited by the presence of free 7-methylguanosine [14]. The dependency of splicing on the 5′ cap is mediated by the cap-binding complex, which is a heteromeric complex formed by cap-binding protein (CBP) 80 and CBP20. From yeast to humans, the 5′ cap is necessary for the translation of almost all mRNAs, with the exception of mRNAs translated by an internal ribosome entry site [15]. The presence of a 5′ cap can also protect mRNA from degradation in *X. laevis* [16–18], while in *S. cerevisiae* inhibition of guanosine capping *in vivo* provoked rapid degradation in some but not all mRNAs, demonstrating the necessity for a guanosine cap to stabilize at a least a subset of mRNAs [4, 7, 19, 20]. Similarly, mRNA polyadenylation and nuclear export appear to largely be independent of the 5′ capping in *S. cerevisiae* [3] but dependent in other species such as *X. laevis* and humans [6, 21]. Thus, while the influence of 5′ capping is pivotal for subsequent mRNA biogenic steps such as transcriptional elongation, pre-mRNA splicing, and translation, species-specific differences seem to occur for degradation protection and mRNA polyadenylation. Given the essential role of 5′ capping in basal mRNA biogenesis, to date no specific defects affecting heart morphogenesis and/or muscle development have been reported.

13.2.2 3′ End Polyadenylation

Polyadenylation is a two-step nuclear process that involves an endonucleolytic cleavage of the pre-mRNA at the 3′-end and the polymerization of a poly-adenosine (polyA) tail (Fig. 13.1), which is fundamental for mRNA stability, nuclear export, and efficient translation during development [22]. The core molecular machinery responsible for the definition of a poly-A site includes several recognition, cleavage, and polyadenylation factors that identify and act on a given poly-A signal present in a pre-mRNA, usually an AAUAAA hexamer [22]. This mechanism is tightly regulated by both cis- and trans-acting factors, and its impairment can cause inefficient gene expression and thus disease. Previous studies have indicated that more than half of the human genes possess multiple polyadenylation sites [23], dubbed APA, which may produce mRNA isoforms with different protein-coding regions or 3′ UTRs of variable length. Interestingly, such a property is also documented in yeast [24]. The differential recognition of polyadenylation signals leads to long or short 3′ UTR of the transcripts. Usage of alternative poly(A) sites influences the fate of mRNAs by altering the availability of RNA-binding protein sites and miRNA binding sites. Abnormalities in the 3′-end processing mechanisms thus represent a common feature among many oncological, immunological, neurological, and hematological disorders [23, 25, 26], and the usage of APA and alterations in polyadenylation are beginning to be discovered and studied in human diseases [27, 28], yet to date no direct involvement in cardiovascular diseases has been reported.

13.2.3 Nonsense-Mediated Decay

Nonsense-mediated decay (NMD) is an evolutionary conserved surveillance pathway present in all eukaryotes studied to date. NMD plays an important role in the posttranscriptional control of gene expression. Approximately one-third of human genes generate pre-mRNAs that undergo alternative splicing, and similarly one-third of alternatively spliced transcripts are targeted for elimination by the NMD pathway [29]. Most alternatively spliced NMD targets appear to be generated in error [30], yet NMD also downregulates the level of other apparently normal transcripts [31–33]. NMD targets premature translation termination codons (PTC)-containing transcripts for rapid degradation (Fig. 13.1), thus protecting the organism from deleterious gain- or loss-of-function (dominant-negative effects) effects of the resulting truncated proteins [34–36]. As a rule, NMD degrades newly synthesized mRNAs during a pioneer round of translation [37–40] and occurs when a PTC is located more than 50–55 nucleotides upstream of the last exon-exon junction within the mRNA, and at least one intron and components of translation are present [41]. Importantly, there is a growing body of evidence supporting that mRNA decay in eukaryotes requires an exit from translation so that the mRNA is accessible to degradative activities [42–45].

The role of NMD in genetic diseases is emerging progressively. A pivotal role for NMD in cystic fibrosis as well as in Duchenne muscular dystrophy (DMD) has been documented (see for a review [46]), yet has only begun to be recognized in cardiac genetic diseases. Geiger et al. [47] recently reported that insufficient clearance of lamin A/C truncated mutations by NMD underlies the development of dilated cardiomyopathy in a human kindred. Similar findings have also been reported for nonsense mutations in hERG in the context of human long QT syndrome [48, 49]. Importantly an intricate relationship between NMD and the ubiquitin-proteasome system has been recently demonstrated in the context of hypertrophic cardiomyopathy [50], opening new ways to understand the complex RNA-protein interphase. In the context of congenital heart diseases, involvement of NMD has been proven for GATA binding protein 6 (*GATA6*) regulation in the setting of ventricular septal defect, patent ductus arteriosus, and congenital diaphragmatic hernia [51] and suspected in a kindred of syndromic patent ductus arteriosus as consequence the generation of aberrant transcription factor AP-2 beta (*TFAP2B*) splice variants [52].

13.3 mRNA Maturation: Generating Diversity (RNA Editing and Pre-mRNA Splicing)

13.3.1 RNA Editing

RNA editing relates to those molecular processes by which the RNA nucleotide sequence is conspicuously modified (Fig. 13.1). To date such changes have been observed in tRNA, rRNA, and mRNA molecules of eukaryotes, but not prokaryotes. RNA editing can modify an A-to-I (inosine) by the action of adenosine deaminase

that acts on RNA (ADAR), and similarly a C-to-U modification can be elicited by a protein complex composed by APOBEC-1 (apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1), an RNA cytidine deaminase, and APOBEC-1 complementation factor (ACF). This C to U editing holoenzyme (APOBEC-1/ACF) is also in part regulated by CELF2 [53, 54].

Inosine is an essential modification introduced by specialized enzymes in a highly regulated manner generating thereafter transcriptome diversity. Adenosine to inosine (A-to-I) modification by the ADAR (i.e., ADAR1 and ADAR2) enzymes performs the most common type of RNA editing in metazoans [55], while C-to-U modifications seem to be confined to more discrete transcripts [53, 56–59]. A-to-I RNA editing most frequently targets repetitive RNA sequences located within introns and 5′ and 3′ untranslated regions (UTRs). ADARs use double-stranded RNA as substrates but allow structure interruptions such as bulges and loops. It is well known that these enzymes can use messenger RNA as targets for A-to-I editing and thereby recode the transcript. Both ADAR1 and ADAR2 have been proven to be able to also target short double-stranded RNA molecules, i.e., microRNAs and their precursors. Since the editing activity is found both in the nucleus and the cytoplasm, there are several steps during the microRNA maturation pathway that can be targeted for modification [60]. Although the biological significance of non-coding RNA editing remains largely unknown, several possibilities have been proposed, including its role in the control of endogenous short interfering RNAs [61].

RNA editing involving C-to-U modifications has been reported extensively to play a pivotal role in virus-associated human diseases, including human T lymphotropic virus (HTLV), hepatitis C virus (HCV), hepatitis B virus (HBV), and Epstein-Barr virus (EBV), among others [62, 63]. Furthermore, more recently a possible role in cancer development has also been proposed [63]. However, to date, no abnormalities in C-to-U RNA editing have been reported in cardiovascular diseases.

A-to-I RNA defective editing has been reported in various human diseases including viral infection susceptibility and cancer and neurological and psychiatric disorders [64–68]. Involvement of defective RNA editing in cardiovascular diseases is indirect and scarce [69, 70], yet an involvement in congenital heart diseases is likely to soon emerge.

13.3.2 Pre-mRNA Splicing and Alternative Splicing

RNA splicing is the molecular process by which introns are deleted from nascent immature mRNA providing the means to successfully liked exons back together and thus form a single mature mRNA molecule. RNA splicing is carried out by the assembly of over a hundred core proteins and five small nuclear RNAs into large ribonucleoprotein complexes, named spliceosomes [71]. Regulation of splicing is a complex process [72–74], and alterations of splicing potential have major consequences in distinct human diseases [75].

Alternative splicing is a major driver of protein diversity and allows the generation of distinct proteins from a single gene. It is estimated that almost 85 % of genes within the human genome undergo alternative splicing. Distinct mechanisms such as exon exclusion, intron retention, and the usage of alternative splice sites contribute to modify protein structure, localization, regulation, and function [76, 77]. Interestingly, genetic mutations in distinct spliceosome components have been reported in human families with distinct cardiac diseases such as myocardial infarction [78, 79] and dilated cardiomyopathy [80, 81], suggesting a functional link. Importantly, alternative splicing also plays a pivotal role during embryonic development. Differential expression of distinct spliceosome components has been reported during heart development [82]. Postnatal excitation-contraction coupling impairment has been reported in genetically engineered mice lacking ASF/SF2 spliceosome component [83], and mutant mice for SRp38, a spliceosome regulator, display early embryonic cardiac resulting in impaired calcium handling [84].

On the other hand, alternatively spliced variants have been documented widely in cardiovascular diseases such as cardiomyopathies, arrhythmias, and vascular defects leading to differential expression of sarcomeric proteins, ion channels, and cell signaling proteins [76, 77, 85–89]. An example of the impact of alternative splicing in adult heart physiology is illustrated by the diversity and functional consequences of alternative spliced variants of the troponin-tropomyosin complex (see for a review [90]). Multiple alternatively spliced variants are formed from each of the troponin isoforms, and deregulation of spliced variant expression is linked to dilated cardiomyopathy in different species [91–93]. Similarly, impaired ion channel splice variants also contribute to cardiac arrhythmogenesis, as reported for distinct components of the calcium handling and plasma membrane cardiac pumps [86, 88].

Multiple transcription factors, with critical roles in cardiac development, are alternatively spliced, such as T-box genes [94–96], myocardin [97], myocyte enhancer factor (Mef)-2 [98, 99], pituitary homeobox (Pitx)-2 [100–102], and GATA binding protein 4 (Gata4) [103]. In this context, Yehya et al. [104] identified an intronic retention variant of the *NFATC1* (nuclear factor of activated T cells, cytoplasmic, calcineurin-dependent 1) gene in patients with ventricular septal defects, suggesting that such a spliced variant might be a VSD-susceptibility gene. Bedard et al. [105] reported spliced variants of *ZIC3* (Zic family member 3) linked to patients with heterotaxy and congenital heart diseases. McCright et al. [106] reported that aberrant Notch2 alternative spliced variants leads to myocardial hypoplasia as well as eye and kidney defects. More recently, Ricci et al. [107] demonstrate that multiple genes were differentially spliced in hypoplastic left heart syndrome, suggesting a deregulation of cell metabolism and cytoskeleton and cell adherence. Interestingly, impaired alternative splicing in other genes also result in cardiac alterations. Impaired fibronectin splicing is associated with thoracic aortic aneurysm in patients with bicuspid aortic valve [108], while abnormal *SCN5A* (sodium channel, voltage gated, type V, alpha subunit) alternative spliced variants leads to fetal arrhythmias [109]. Furthermore, impaired expression of alternatively spliced *NXT2* (nuclear transport factor 2-like export factor 2) variants, a protein

involved in nuclear RNA export, also has been proven to affect cardiac development, particularly valve formation [110]. Ver Heyen et al. [111] reported that genetic engineered disruption of *SERCA2a/2b* (sarcoplasmic/endoplasmic reticulum calcium ATPase 2a/b) alternative splicing leads to 20 % increase in embryonic and neonatal mortality, as consequence of severe cardiac malformations. Buyon et al. [112] describes a spliced variant of congenital heart block-associated 52 kb autoantigen which is maximal at the time of fetal heart block, suggesting a putative role in its pathophysiology. These reports exemplify the potential causative role of impaired alternative spliced variants as key regulatory modulators of cardiac development. Increasing evidence of this is expected in the coming years as deep-sequencing technologies depict the magnitude of the alternative spliced transcriptome in congenital heart diseases.

13.4 Non-coding RNA-Mediated Posttranscriptional Control

Non-coding RNAs (ncRNAs) constitute a highly diverse group of RNA molecules in structure and function (see for a recent review [113]). Currently ncRNAs are broadly classified according to their size. Small ncRNAs are generally defined as those that are <200 nucleotides, whereas long non-coding RNAs (lncRNAs) can extend to tens or even hundreds of thousands of nucleotides in length. Small ncRNAs display a rather homogeneous structure, whereas lcnRNAs have more complex secondary structures. ncRNAs, such as ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs), have been extensively studied given their prominent roles as components of the translational machinery. A similar situation occurs with small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs) given their essential role in splicing. Over the last decade, great interest has arisen in a class of small regulatory ncRNAs that directly affect the expression and/or function of protein-coding genes, i.e., microRNAs (miRNAs). miRNAs were discovered in the early 1990s and since then represent the most extensively studied class of ncRNA. microRNAs display an average length of 22–24 nucleotides and are capable of interacting with the 3′ untranslated region of coding RNAs (mRNAs) eliciting blockage of protein translation and/or mRNA degradation [114]. Understanding of microRNA biogenesis has moved rapidly [115], whereas insights into the functional role of microRNAs are progressively emerging at a slower pace. Nonetheless, the functional relevance of distinct microRNAs in multiple aspects of cardiac development and diseases is now widely documented (see for recent reviews [116–118]).

Differential expression of microRNAs has been documented widely during embryonic [119–121], postnatal [122, 123], and the aging heart [124, 125] suggesting a pivotal role for microRNAs during different stages of heart development. Similarly, investigators have reported impaired microRNA expression in a large variety of cardiovascular physiopathological conditions, such as hypertrophic and/or dilated cardiomyopathy [126–131], heart failure [132–134], atrial fibrillation [135–139], and aortic aneurism [140]. The importance of microRNAs in congenital heart diseases is manifested by the embryonic defects observed in genetically engineered

mice. Conditional deletion of Dicer, an endonuclease required for the microRNA processing, with distinct Cre drivers, demonstrated the critical role of microRNA biogenesis in distinct temporal and tissue-specific contexts during cardiovascular development. Conditional ablation using an early cardiogenic deletor mouse strain (*Nkx2-5-Cre* mice) led to embryonic lethality due to cardiac hypoplasia [141], whereas ablation with myocardial-specific Cre driver line *(αMHC-Cre*) resulted in outflow tract defects and impaired chamber formation [142]. More recently Singh et al. [143] demonstrated that Dicer deletion in pro-epicardial cells compromised cardiac vascular development. In addition, germline deletion of discrete microRNAs such as miR-1-2 resulted in ventricular septal defects and early embryonic lethality [141], whereas miR-126 deletion leads to embryonic lethality due to vascular leakage [144]. These studies highlight the importance of microRNA biology for congenital heart diseases. In this context, an increasing number of studies are providing the impaired microRNA signature of distinct congenital heart diseases [145], such as ventricular septal defects [146], tetralogy of Fallot [147], corrected transposition of great arteries [148], univentricular left hearts [149], bicuspid aortic valves [150], and DiGeorge syndrome [151]. These studies provide novel insights for the prospective use of microRNA signature as biomarkers of prenatal diagnosis [152, 153]. However, in most cases, the impaired regulatory networks modulated by these microRNAs remain to be fully elucidated. In the coming years, we shall see an explosion on the understanding and functional consequences of microRNA regulation, with great hopes as to their therapeutic potential, including pediatric cardiology [154].

In addition to microRNAs, lncRNAs and circular RNAs are emerging also as post-transcriptional modulators. lcnRNAs might undergo alternative splicing and in some cases, but not in others, can be polyadenylated. lncRNAs can be located within the nucleus but also can be found within the cytoplasm thus potentially exerting a large number of biological functions. lncRNAs have been reported in a wide range of functions beyond posttranscriptional regulation such as cell cycle progression, differentiation, apoptosis, structural or cellular trafficking, as well as serving as precursors for smaller RNAs (see for a recent reviews [113, 154–156]). Differential expression of lncRNAs has been reported in the developing [157–159], adult [160] and aging [161] heart as well as in ventricular cardiac hypertrophy [161], heart failure [134], myocardial infarction [162], and cardiac ischemia [163]. Interestingly, a pivotal role of *myheart* lcnRNA has been reported in the context of cardiac hypertrophy [164, 165]. Importantly, differentially expression of lcnRNAs also has been reported in hearts with congenital heart defects, such as ventricular septal defect [166] and tetralogy of Fallot [167]. Overall these data suggest a plausible role for lncRNAs in congenital heart diseases, and the first evidences for this have recently been reported. Seminal works demonstrated that genetic deletion of *fendrr* and *braveheart*, two cardiac enriched lncRNAs, respectively, leads to impaired cardiogenesis [168, 169]. On the other hand, understanding of the functional role of circular RNAs is very incipient, with yet some evidence that they can act as microRNA sponges [170, 171]. In the coming years, it is expected that unraveling the functional roles of lcnRNAs and circular RNAs will guide toward the understanding of the etiology of distinct cardiovascular diseases, including there in congenital heart diseases.

Conclusion

Posttranscriptional regulation is a complex process. This chapter has highlighted distinct processes that sequentially modify the nascent mRNA molecule into a mature form with, in many cases multiple distinct variants. It is important to emphasize that complex regulatory networks between these processes are well documented such as for the multiple roles of 5′ capping and 3′ polyadenylation in mRNA stabilization, elongation, and translation among others, but importantly emerging evidence demonstrates that microRNAs and lncRNAs also participate in these intricately interlinked regulatory mechanisms [172], i.e., modulating alternative splicing [173]. Thus, we could foresee that in coming years, impaired posttranscriptional regulatory networks would be linked to distinct congenital heart diseases, as recently reported by Xu et al. [174].

References

1. Lukong KE, Chang KW, Khandjian EW et al (2008) RNA-binding proteins in human genetic disease. Trends Genet 24:416–425
2. Blech-Hermoni Y, Ladd AN (2013) RNA binding proteins in the regulation of heart development. Int J Biochem Cell Biol 45:2467–2478
3. Forget A, Chartrand P (2011) Cotranscriptional assembly of mRNP complexes that determine the cytoplasmic fate of mRNA. Transcription 2:86–90
4. Fresco LD, Buratowski S (1996) Conditional mutants of the yeast mRNA capping enzyme show that the cap enhances, but is not required for, mRNA splicing. RNA 2:584–596
5. Shatkin AJ, Manley JL (2000) The ends of the affair: capping and polyadenylation. Nat Struct Biol 7:838–842
6. Glover-Cutter K, Kim S, Espinosa J et al (2008) RNA polymerase II pauses and associates with pre-mRNA processing factors at both ends of genes. Nat Struct Mol Biol 15:71–78
7. Cowling VH (2009) Regulation of mRNA cap methylation. Biochem J 425:295–302
8. Suh MH, Meyer PA, Gu M et al (2010) A dual interface determines the recognition of RNA polymerase II by RNA capping enzyme. J Biol Chem 285:34027–34038
9. Yue Z, Maldonado E, Pillutla R et al (1997) Mammalian capping enzyme complements mutant Saccharomyces cerevisiae lacking mRNA guanylyltransferase and selectively binds the elongating form of RNA polymerase II. Proc Natl Acad Sci U S A 94:12898–12903
10. Tsukamoto T, Shibagaki Y, Niikura Y et al (1998) Cloning and characterization of three human cDNAs encoding mRNA (guanine-7-)-methyltransferase, an mRNA cap methylase. Biochem Biophys Res Commun 251:27–34
11. Yamada-Okabe T, Doi R, Shimmi O et al (1998) Isolation and characterization of a human cDNA for mRNA 5′-capping enzyme. Nucleic Acids Res 26:1700–1706
12. Pillutla RC, Shimamoto A, Furuichi Y et al (1998) Human mRNA capping enzyme (RNGTT) and cap methyltransferase (RNMT) map to 6q16 and 18p11.22-p11.23, respectively. Genomics 1998(54):351–353
13. Ishikawa K, Nagase T, Nakajima D et al (1997) Prediction of the coding sequences of unidentified human genes. VIII. 78 new cDNA clones from brain which code for large proteins in vitro. DNA Res 4:307–313
14. Konarska MM, Padgett RA, Sharp PA (1984) Recognition of cap structure in splicing in vitro of mRNA precursors. Cell 38:731–736
15. Spriggs KA, Stoneley M, Bushell M et al (2008) Re-programming of translation following cell stress allows IRES-mediated translation to predominate. Biol Cell 100:27–38
16. Furuichi Y, LaFiandra A, Shatkin AJ (1977) 5′-Terminal structure and mRNA stability. Nature 266:235–239

17. Shimotohno K, Kodama Y, Hashimoto J et al (1977) Importance of 5′-terminal blocking structure to stabilize mRNA in eukaryotic protein synthesis. Proc Natl Acad Sci U S A 74:2734–2738
18. Murthy KG, Park P, Manley JL (1991) A nuclear micrococcal-sensitive, ATP-dependent exoribonuclease degrades uncapped but not capped RNA substrates. Nucleic Acids Res 19:2685–2692
19. Schwer B, Shuman S (1996) Conditional inactivation of mRNA capping enzyme affects yeast pre-mRNA splicing in vivo. RNA 2:574–583
20. Schwer B, Mao X, Shuman S (1998) Accelerated mRNA decay in conditional mutants of yeast mRNA capping enzyme. Nucleic Acids Res 26:2050–2057
21. Flaherty SM, Fortes P, Izaurralde E et al (1997) Participation of the nuclear cap binding complex in pre-mRNA 3′ processing. Proc Natl Acad Sci U S A 94:11893–11898
22. Curinha A, Braz SO, Pereira-Castro I et al (2014) Implications of polyadenylation in health and disease. Nucleus 5:508–519
23. Tian B, Hu J, Zhang H, Lutz CS (2005) A large-scale analysis of mRNA polyadenylation of human and mouse genes. Nucleic Acids Res 33:201–212
24. Pelechano V, Wei W, Steinmetz LM (2013) Extensive transcriptional heterogeneity revealed by isoform profiling. Nature 497:127–131
25. Carpenter S, Ricci EP, Mercier BC et al (2014) Post-transcriptional regulation of gene expression in innate immunity. Nat Rev Immunol 14:361–376
26. Griseri P, Pagès G (2014) Regulation of the mRNA half-life in breast cancer. World J Clin Oncol 5:323–334
27. Chatterjee S, Pal JK (2009) Role of 5′- and 3′-untranslated regions of mRNAs in human diseases. Biol Cell 101:251–262
28. Rehfeld A, Plass M, Krogh A et al (2013) Alterations in polyadenylation and its implications for endocrine disease. Front Endocrinol 4:53
29. Lewis BP, Green RE, Brenner SE (2003) Evidence for the widespread coupling of alternative splicing and nonsense-mediated mRNA decay in humans. Proc Natl Acad Sci U S A 100:189–192
30. Pan Q, Saltzman AL, Kim YK et al (2006) Quantitative microarray profiling provides evidence against widespread coupling of alternative splicing with nonsense-mediated mRNA decay to control gene expression. Genes Dev 20:153–158
31. Mendell JT, Sharifi NA, Meyers JL et al (2004) Nonsense surveillance regulates expression of diverse classes of mammalian transcripts and mutes genomic noise. Nat Genet 36:1073–1078
32. Wittmann J, Hol EM, Jäck HM (2006) hUPF2 silencing identifies physiologic substrates of mammalian nonsense-mediated mRNA decay. Mol Cell Biol 26:1272–1287
33. Ni JZ, Grate L, Donohue JP et al (2007) Ultraconserved elements are associated with homeostatic control of splicing regulators by alternative splicing and nonsense-mediated decay. Genes Dev 21:708–718
34. Chang YF, Imam JS, Wilkinson MF (2007) The nonsense-mediated decay RNA surveillance pathway. Annu Rev Biochem 76:51–74
35. Maquat LE (2005) Nonsense-mediated mRNA decay in mammals. J Cell Sci 118:1773–1776
36. Garneau NL, Wilusz J, Wilusz CJ (2007) The highways and byways of mRNA decay. Nat Rev Mol Cell Biol 8:113–126
37. Ishigaki Y, Li X, Serin G, Maquat LE (2001) Evidence for a pioneer round of mRNA translation: mRNAs subject to nonsense-mediated decay in mammalian cells are bound by CBP80 and CBP20. Cell 106:607–617
38. Lejeune F, Ishigaki Y, Li X, Maquat LE (2002) The exon junction complex is detected on CBP80-bound but not eIF4E-bound mRNA in mammalian cells: dynamics of mRNP remodeling. EMBO J 21:3536–3545
39. Lejeune F, Ranganathan AC, Maquat LE (2004) eIF4G is required for the pioneer round of translation in mammalian cells. Nat Struct Mol Biol 11:992–1000

40. Chiu SY, Lejeune F, Ranganathan AC et al (2004) The pioneer translation initiation complex is functionally distinct from but structurally overlaps with the steady-state translation initiation complex. Genes Dev 18:745–754
41. Zhang J, Sun X, Qian Y et al (1998) At least one intron is required for the nonsense-mediated decay of triosephosphate isomerase mRNA: a possible link between nuclear splicing and cytoplasmic translation. Mol Cell Biol 18:5272–5283
42. Coller J, Parker R (2004) Eukaryotic mRNA decapping. Annu Rev Biochem 73:861–890
43. Coller J, Parker R (2005) General translational repression by activators of mRNA decapping. Cell 122:875–886
44. Ferraiuolo MA, Basak S, Dostie J et al (2005) A role for the eIF4E-binding protein 4E-T in P-body formation and mRNA decay. Cell Biol 170:913–924
45. Braun KA, Young ET (2014) Coupling mRNA synthesis and decay. Mol Cell Biol 34:4078–4087
46. Linde L, Kerem B (2008) Introducing sense into nonsense in treatments of human genetic diseases. Trends Genet 24:552–563
47. Geiger SK, Bar H, Ehlermann P et al (2008) Incomplete nonsense-mediated decay of mutant lamin A/C mRNA provokes dilated cardiomyopathy and ventricular tachycardia. J Mol Med 86:281–289
48. Gong Q, Zhang L, Vincent GM et al (2007) Nonsense mutations in hERG cause a decrease in mutant mRNA transcripts by nonsense-mediated mRNA decay in human long-QT syndrome. Circulation 116:17–24
49. Zarraga IG, Zhang L, Stump MR et al (2011) Nonsense-mediated mRNA decay caused by a frameshift mutation in a large kindred of type 2 long QT syndrome. Heart Rhythm 8:1200–1206
50. Vignier N, Schlossarek S, Fraysse B et al (2009) Nonsense-mediated mRNA decay and ubiquitin-proteasome system regulate cMyBP-C mutant levels in cardiomyopathic mice. Circ Res 105:239–248
51. Suzuki S, Nakao A, Sarhat AR et al (2014) A case of pancreatic agenesis and congenital heart defects with a novel GATA6 nonsense mutation: evidence of haploinsufficiency due to nonsense-mediated mRNA decay. Am J Med Genet A 2014(164A):476–479
52. Mani A, Radhakrishnan J, Farhi A et al (2005) Syndromic patent ductus arteriosus: evidence for haploinsufficient TFAP2B mutations and identification of a linked sleep disorder. Proc Natl Acad Sci U S A 102:2975–2979
53. Chen Z, Eggerman TL, Patterson AP (2007) ApoB mRNA editing is mediated by a coordinated modulation of multiple apoB mRNA editing enzyme components. Am J Physiol Gastrointest Liver Physiol 292:G53–G65
54. Wedekind JE, Dance GS, Sowden MP et al (2003) Messenger RNA editing in mammals: new members of the APOBEC family seeking roles in the family business. Trends Genet 19:207–216
55. Galeano F, Tomaselli S, Locatelli F et al (2012) A-to-I RNA editing: the "ADAR" side of human cancer. Semin Cell Dev Biol 23:244–250
56. Anant S, Henderson J, Mukhopadhyay D et al (2001) Novel role for RNA-binding protein CUGBP2 in mammalian RNA editing. J Biol Chem 276:47338–47351
57. Blanc V, Davidson NO (2003) C-to-U RNA editing: mechanisms leading to genetic diversity. J Biol Chem 278:1395–1398
58. Zhang H (2010) The inhibitory effect of apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3G (APOBEC3G) and its family members on the activity of cellular microRNAs. Prog Mol Subcell Biol 50:71–83
59. Dasgupta T, Ladd AN (2012) The importance of CELF control: molecular and biological roles of the CUG-BP, Elav-like family of RNA-binding proteins. Wiley Interdiscip Rev RNA 3:104–121
60. Ohman M (2007) A-to-I editing challenger or ally to the microRNA process. Biochimie 89:1171–1176
61. Nishikura K (2010) Functions and regulation of RNA editing by ADAR deaminases. Annu Rev Biochem 79:321–349

62. Franca R, Spadari S, Maga G (2006) APOBEC deaminases as cellular antiviral factors: a novel natural host defense mechanism. Med Sci Monit 12:RA92–RA98
63. Vieira VC, Soares MA (2013) The role of cytidine deaminases on innate immune responses against human viral infections. Biomed Res Int 2013:683095
64. van den Hoogen BG, van Boheemen S, de Rijck J et al (2014) Excessive production and extreme editing of human metapneumovirus defective interfering RNA is associated with type I IFN induction. J Gen Virol 95:1625–1633
65. Sarvestani ST, Tate MD, Moffat JM et al (2014) Inosine-mediated modulation of RNA sensing by Toll-like receptor 7 (TLR7) and TLR8. J Virol 88:799–810
66. Clerzius G, Shaw E, Daher A et al (2013) The PKR activator, PACT, becomes a PKR inhibitor during HIV-1 replication. Retrovirology 10:96
67. Avesson L, Barry G (2014) The emerging role of RNA and DNA editing in cancer. Biochim Biophys Acta 1845:308–316
68. Dominissini D, Moshitch-Moshkovitz S, Amariglio N et al (2011) Adenosine-to-inosine RNA editing meets cancer. Carcinogenesis 2011(32):1569–1577
69. Li D, Bachinski L, Roberts R (2001) Genomic organization and isoform-specific tissue expression of human NAPOR (CUGBP2) as a candidate gene for familial arrhythmogenic right ventricular dysplasia. Genomics 74:396–401
70. Lichtner P, Attié-Bitach T, Schuffenhauer S et al (2002) Expression and mutation analysis of *Brunol3*, a candidate gene for heart and thymus developmental defects associated with partial monosomy 10p. J Mol Med 80:431–442
71. Wang Z, Burge CB (2008) Splicing regulation: from a parts list of regulatory elements to an integrated splicing code. RNA 14:802–813
72. Burge CB, Tuschl T, Sharp PA (1999) Splicing of precursors to mRNAs by the spliceosomes. In: Gesteland RF et al (eds) The RNA world. Cold Spring Harbor Press, Cold Spring Harbor, pp 525–560
73. Hastings ML, Krainer AR (2001) Pre-mRNA splicing in the new millennium. Curr Opin Cell Biol 13:302–309
74. Black DL (2003) Mechanisms of alternative pre-messenger RNA splicing. Annu Rev Biochem 72:291–336
75. Nissim-Rafinia M, Kerem B (2002) Splicing regulation as a potential genetic modifier. Trends Genet 18:123–127
76. Han J, Xiong J, Wang D et al (2011) Pre-mRNA splicing: where and when in the nucleus. Trends Cell Biol 21:336–343
77. Lara-Pezzi E, Gómez-Salinero J, Gatto A, García-Pavía P (2013) The alternative heart: impact of alternative splicing in heart disease. J Cardiovasc Transl Res 6:945–955
78. Ria M, Eriksson P, Boquist S et al (2006) Human genetic evidence that OX40 is implicated in myocardial infarction. Biochem Biophys Res Commun 339:1001–1006
79. Maatz H, Jens M, Liss M et al (2014) RNA-binding protein RBM20 represses splicing to orchestrate cardiac pre-mRNA processing. J Clin Invest 124:3419–3430
80. Brauch KM, Karst ML, Herron KJ et al (2009) Mutations in ribonucleic acid binding protein gene cause familial dilated cardiomyopathy. J Am Coll Cardiol 54:930–941
81. Rimessi P, Fabris M, Bovolenta M et al (2010) Antisense modulation of both exonic and intronic splicing motifs induces skipping of a DMD pseudo-exon responsible for x-linked dilated cardiomyopathy. Hum Gene Ther 21:1137–1146
82. Ruiz-Lozano P, Doevendans P, Brown A et al (1997) Developmental expression of the murine spliceosome-associated protein mSAP49. Dev Dyn 208:482–490
83. Xu X, Yang D, Ding JH et al (2005) ASF/SF2-regulated CaMKIIdelta alternative splicing temporally reprograms excitation-contraction coupling in cardiac muscle. Cell 120:59–72
84. Feng Y, Valley MT, Lazar J et al (2009) SRp38 regulates alternative splicing and is required for Ca(2+) handling in the embryonic heart. Dev Cell 16:528–538
85. Dally S, Corvazier E, Bredoux R et al (2010) Multiple and diverse coexpression, location, and regulation of additional SERCA2 and SERCA3 isoforms in nonfailing and failing human heart. J Mol Cell Cardiol 48:633–644

86. Schroeter A, Walzik S, Blechschmidt S et al (2010) Structure and function of splice variants of the cardiac voltage-gated sodium channel Na(v)1.5. J Mol Cell Cardiol 49:16–24
87. Valadkhan S, Jaladat Y (2010) The spliceosomal proteome: at the heart of the largest cellular ribonucleoprotein machine. Proteomics 10:4128–4141
88. Zhang SS, Shaw RM (2013) Multilayered regulation of cardiac ion channels. Biochim Biophys Acta 1833:876–885
89. Kjellqvist S, Maleki S, Olsson T et al (2013) A combined proteomic and transcriptomic approach shows diverging molecular mechanisms in thoracic aortic aneurysm development in patients with tricuspid- and bicuspid aortic valve. Mol Cell Proteomics 12:407–425
90. Sheng JJ, Jin JP (2014) Gene regulation, alternative splicing, and posttranslational modification of troponin subunits in cardiac development and adaptation: a focused review. Front Physiol 5:165
91. Biesiadecki BJ, Elder BD, Yu ZB, Jin JP (2002) Cardiac troponin T variants produced by aberrant splicing of multiple exons in animals with high instances of dilated cardiomyopathy. J Biol Chem 277:50275–50285
92. Biesiadecki BJ, Jin JP (2002) Exon skipping in cardiac troponin T of turkeys with inherited dilated cardiomyopathy. J Biol Chem 277:18459–18468
93. Wei B, Gao J, Huang XP, Jin JP (2010) Mutual rescues between two dominant negative mutations in cardiac troponin I and cardiac troponin T. J Biol Chem 285:27806–27816
94. Hoogaars WM, Barnett P, Rodriguez M et al (2008) TBX3 and its splice variant TBX3 + exon 2a are functionally similar. Pigment Cell Melanoma Res 21:379–387
95. Georges R, Nemer G, Morin M et al (2008) Distinct expression and function of alternatively spliced Tbx5 isoforms in cell growth and differentiation. Mol Cell Biol 28:4052–4067
96. DeBenedittis P, Jiao K (2011) Alternative splicing of T-box transcription factor genes. Biochem Biophys Res Commun 412:513–517
97. Ueyama T, Kasahara H, Ishiwata T et al (2003) Myocardin expression is regulated by Nkx2.5, and its function is required for cardiomyogenesis. Mol Cell Biol 23:9222–9232
98. Iida K, Hidaka K, Takeuchi M et al (1999) Expression of MEF2 genes during human cardiac development. Tohoku J Exp Med 187:15–23
99. Zhu B, Gulick T (2004) Phosphorylation and alternative pre-mRNA splicing converge to regulate myocyte enhancer factor 2C activity. Mol Cell Biol 24:8264–8275
100. Schweickert A, Campione M, Steinbeisser H et al (2000) Pitx2 isoforms: involvement of Pitx2c but not Pitx2a or Pitx2b in vertebrate left-right asymmetry. Mech Dev 90:41–51
101. Yu X, St Amand TR, Wang S et al (2001) Differential expression and functional analysis of Pitx2 isoforms in regulation of heart looping in the chick. Development 128:1005–1013
102. Lamba P, Hjalt TA, Bernard DJ (2008) Novel forms of Paired-like homeodomain transcription factor 2 (PITX2): generation by alternative translation initiation and mRNA splicing. BMC Mol Biol 9:31
103. Mazaud Guittot S, Bouchard MF, Robert-Grenon JP et al (2009) Conserved usage of alternative 5′ untranslated exons of the GATA4 gene. PLoS One 4(12):e8454
104. Yehya A, Souki R, Bitar F et al (2006) Differential duplication of an intronic region in the NFATC1 gene in patients with congenital heart disease. Genome 49:1092–1098
105. Bedard JE, Haaning AM, Ware SM (2011) Identification of a novel ZIC3 isoform and mutation screening in patients with heterotaxy and congenital heart disease. PLoS One 6(8):e23755
106. McCright B, Gao X, Shen L et al (2001) Defects in development of the kidney, heart and eye vasculature in mice homozygous for a hypomorphic Notch2 mutation. Development 128:491–502
107. Ricci M, Xu Y, Hammond HL et al (2012) Myocardial alternative RNA splicing and gene expression profiling in early stage hypoplastic left heart syndrome. PLoS One 7(1):e29784
108. Paloschi V, Kurtovic S, Folkersen L et al (2011) Impaired splicing of fibronectin is associated with thoracic aortic aneurysm formation in patients with bicuspid aortic valve. Arterioscler Thromb Vasc Biol 31:691–697
109. Murphy LL, Moon-Grady AJ, Cuneo BF et al (2012) Developmentally regulated SCN5A splice variant potentiates dysfunction of a novel mutation associated with severe fetal arrhythmia. Heart Rhythm 9:590–597

110. Huang H, Zhang B, Hartenstein PA et al (2005) NXT2 is required for embryonic heart development in zebrafish. BMC Dev Biol 5:7
111. Ver Heyen M, Heymans S, Antoons G et al (2001) Replacement of the muscle-specific sarcoplasmic reticulum Ca(2+)-ATPase isoform SERCA2a by the nonmuscle SERCA2b homologue causes mild concentric hypertrophy and impairs contraction-relaxation of the heart. Circ Res 89:838–846
112. Buyon JP, Tseng CE, Di Donato F et al (1997) Cardiac expression of 52beta, an alternative transcript of the congenital heart block-associated 52-kd SS-A/Ro autoantigen, is maximal during fetal development. Arthritis Rheum 40:655–660
113. Schonrock N, Harvey RP, Mattick JS (2012) Long noncoding RNAs in cardiac development and pathophysiology. Circ Res 111:1349–1362
114. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116:281–297
115. Bauersachs J, Thum T (2011) Biogenesis and regulation of cardiovascular microRNAs. Circ Res 109(3):334–347
116. Espinoza-Lewis RA, Wang DZ (2012) MicroRNAs in heart development. Curr Top Dev Biol 100:279–317
117. Chen J, Wang DZ (2012) microRNAs in cardiovascular development. J Mol Cell Cardiol 52:949–957
118. Bonet F, Hernandez-Torres F, Franco D (2014) Towards the therapeutic usage of microRNAs in cardiac disease and regeneration. Exp Clin Cardiol 20:720–756
119. Chinchilla A, Lozano E, Daimi H et al (2011) MicroRNA profiling during mouse ventricular maturation: a role for miR-27 modulating Mef2c expression. Cardiovasc Res 89:98–108
121. Vacchi-Suzzi C, Hahne F, Scheubel P et al (2013) Heart structure-specific transcriptomic atlas reveals conserved microRNA-mRNA interactions. PLoS One 8:e52442
122. Porrello ER, Mahmoud AI, Simpson E et al (2013) Regulation of neonatal and adult mammalian heart regeneration by the miR-15 family. Proc Natl Acad Sci U S A 110:187–192
123. Hsu J, Hanna P, Van Wagoner DR et al (2012) Whole genome expression differences in human left and right atria ascertained by RNA sequencing. Circ Cardiovasc Genet 5:327–335
124. Boon RA, Iekushi K, Lechner S et al (2013) MicroRNA-34a regulates cardiac ageing and function. Nature 495:107–110
125. Dimmeler S, Nicotera P (2013) MicroRNAs in age-related diseases. EMBO Mol Med 5(2):180–190
126. van Rooij E, Sutherland LB, Liu N et al (2006) A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. Proc Natl Acad Sci U S A 103:18255–18260
127. Care A, Catalucci D, Felicetti F et al (2007) MicroRNA-133 controls cardiac hypertrophy. Nat Med 13:613–618
128. Sayed D, Hong C, Chen IY et al (2007) MicroRNAs play an essential role in the development of cardiac hypertrophy. Circ Res 100:416–424
129. Fernandes T, Hashimoto NY, Magalhães FC et al (2011) Aerobic exercise training-induced left ventricular hypertrophy involves regulatory MicroRNAs, decreased angiotensin-converting enzyme-angiotensin ii, and synergistic regulation of angiotensin-converting enzyme 2-angiotensin. Hypertension 58:182–189
130. Yang KC, Ku YC, Lovett M, Nerbonne JM (2012) Combined deep microRNA and mRNA sequencing identifies protective transcriptomal signature of enhanced PI3Kα signaling in cardiac hypertrophy. J Mol Cell Cardiol 53:101–112
131. Reddy S, Zhao M, Hu DQ et al (2012) Dynamic microRNA expression during the transition from right ventricular hypertrophy to failure. Physiol Genomics 44:562–575
132. van Rooij E, Sutherland LB, Thatcher JE et al (2008) Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. Proc Natl Acad Sci U S A 105:13027–13032

133. Drake JI, Bogaard HJ, Mizuno S et al (2011) Molecular signature of a right heart failure program in chronic severe pulmonary hypertension. Am J Respir Cell Mol Biol 45(6):1239–1247
134. Yang KC, Yamada KA, Patel AY et al (2014) Deep RNA sequencing reveals dynamic regulation of myocardial noncoding RNAs in failing human heart and remodeling with mechanical circulatory support. Circulation 129:1009–1021
135. Lu Y, Zhang Y, Wang N et al (2010) MicroRNA-328 contributes to adverse electrical remodeling in atrial fibrillation. Circulation 122:2378–2387
136. Xiao J, Liang D, Zhang Y et al (2011) MicroRNA expression signature in atrial fibrillation with mitral stenosis. Physiol Genomics 43:655–664
137. Cooley N, Cowley MJ, Lin RC et al (2012) Influence of atrial fibrillation on microRNA expression profiles in left and right atria from patients with valvular heart disease. Physiol Genomics 44:211–219
138. Liu Z, Zhou C, Liu Y et al (2012) The expression levels of plasma microRNAs in atrial fibrillation patients. PLoS One 7(9):e44906
139. Nishi H, Sakaguchi T, Miyagawa S et al (2013) Impact of microRNA expression in human atrial tissue in patients with atrial fibrillation undergoing cardiac surgery. PLoS One 8:e73397
140. Liu G, Huang Y, Lu X et al (2010) Identification and characteristics of microRNAs with altered expression patterns in a rat model of abdominal aortic aneurysms. Tohoku J Exp Med 222:187–193
141. Zhao Y, Ransom JF, Li A et al (2007) Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2. Cell 129:303–317
142. Saxena A, Tabin CJ (2010) miRNA-processing enzyme Dicer is necessary for cardiac outflow tract alignment and chamber septation. Proc Natl Acad Sci U S A 107:87–91
143. Singh MK, Lu MM, Massera D et al (2011) MicroRNA-processing enzyme Dicer is required in epicardium for coronary vasculature development. J Biol Chem 286:41036–41045
144. Fish JE, Santoro MM, Morton SU et al (2008) miR-126 regulates angiogenic signaling and vascular integrity. Dev Cell 15:272–284
145. Xing HJ, Li YJ, Ma QM et al (2013) Identification of microRNAs present in congenital heart disease associated copy number variants. Eur Rev Med Pharmacol Sci 17(15):2114–2120
146. Li D, Ji L, Liu L et al (2014) Characterization of circulating microRNA expression in patients with a ventricular septal defect. PLoS One 9:e106318
147. Zhang J, Chang JJ, Xu F et al (2013) MicroRNA deregulation in right ventricular outflow tract myocardium in nonsyndromic tetralogy of fallot. Can J Cardiol 29:1695–1703
148. Lai CT, Ng EK, Chow PC et al (2013) Circulating microRNA expression profile and systemic right ventricular function in adults after atrial switch operation for complete transposition of the great arteries. BMC Cardiovasc Disord 13:73
149. Yu ZB, Han SP, Bai YF et al (2012) microRNA expression profiling in fetal single ventricle malformation identified by deep sequencing. Int J Mol Med 29:53–60
150. Nigam V, Sievers HH, Jensen BC et al (2010) Altered microRNAs in bicuspid aortic valve: a comparison between stenotic and insufficient valves. J Heart Valve Dis 19:459–465
151. de la Morena MT, Eitson JL, Dozmorov IM et al (2013) Signature MicroRNA expression patterns identified in humans with 22q11.2 deletion/DiGeorge syndrome. Clin Immunol 147:11–22
152. Zhu S, Cao L, Zhu J et al (2013) Identification of maternal serum microRNAs as novel noninvasive biomarkers for prenatal detection of fetal congenital heart defects. Clin Chim Acta 424:66–72
153. Yu Z, Han S, Hu P et al (2011) Potential role of maternal serum microRNAs as a biomarker for fetal congenital heart defects. Med Hypotheses 76:424–426
154. Omran A, Elimam D, Webster KA et al (2013) MicroRNAs: a new piece in the paediatric cardiovascular disease puzzle. Cardiol Young 23:642–655
155. Ounzain S, Pezzuto I, Micheletti R et al (2014) Functional importance of cardiac enhancer-associated noncoding RNAs in heart development and disease. J Mol Cell Cardiol 76:55–70

156. Scheuermann JC, Boyer LA (2013) Getting to the heart of the matter: long non-coding RNAs in cardiac development and disease. EMBO J 32:1805–1816
157. Caley DP, Pink RC, Trujillano D et al (2010) Long noncoding RNAs, chromatin, and development. ScientificWorldJournal 10:90–102
158. Zhu S, Hu X, Han S et al (2014) Differential expression profile of long non-coding RNAs during differentiation of cardiomyocytes. Int J Med Sci 11:500–507
159. Zhu JG, Shen YH, Liu HL et al (2014) Long noncoding RNAs expression profile of the developing mouse heart. J Cell Biochem 115:910–918
160. Kaushik K, Leonard VE, Kv S et al (2013) Dynamic expression of long non-coding RNAs (lncRNAs) in adult zebrafish. PLoS One 8:e83616
161. Zhang L, Hamad EA, Vausort M et al (2015) Identification of candidate long noncoding RNAs associated with left ventricular hypertrophy. Clin Transl Sci 8:100–106
162. Ounzain S, Micheletti R, Beckmann T et al (2015) Genome-wide profiling of the cardiac transcriptome after myocardial infarction identifies novel heart-specific long non-coding RNAs. Eur Heart J 36:353–368
163. Liu Y, Li G, Lu H et al (2014) Expression profiling and ontology analysis of long noncoding RNAs in post-ischemic heart and their implied roles in ischemia/reperfusion injury. Gene 543:15–21
164. Liu J, Wang DZ (2014) An epigenetic "LINK(RNA)" to pathological cardiac hypertrophy. Cell Metab 20:555–557
165. Han P, Li W, Lin CH et al (2014) A long noncoding RNA protects the heart from pathological hypertrophy. Nature 514:102–106
166. Song G, Shen Y, Zhu J et al (2013) Integrated analysis of dysregulated lncRNA expression in fetal cardiac tissues with ventricular septal defect. PLoS One 8:e77492
167. O'Brien JE Jr, Kibiryeva N, Zhou XG et al (2012) Noncoding RNA expression in myocardium from infants with tetralogy of Fallot. Circ Cardiovasc Genet 5:279–286
168. Grote P, Wittler L, Hendrix D et al (2013) The tissue-specific lncRNA Fendrr is an essential regulator of heart and body wall development in the mouse. Dev Cell 24:206–214
169. Klattenhoff CA, Scheuermann JC, Surface LE et al (2013) Braveheart, a long noncoding RNA required for cardiovascular lineage commitment. Cell 152:570–583
170. Chen LL, Yang L (2015) Regulation of circRNA biogenesis. RNA Biol 12:381–388
171. Lasda E, Parker R (2014) Circular RNAs: diversity of form and function. RNA 20:1829–1842
172. Matkovich SJ, Edwards JR, Grossenheider TC et al (2014) Epigenetic coordination of embryonic heart transcription by dynamically regulated long noncoding RNAs. Proc Natl Acad Sci U S A 111(33):12264–12269
173. Kalsotra A, Wang K, Li PF et al (2010) MicroRNAs coordinate an alternative splicing network during mouse postnatal heart development. Genes Dev 24:653–658
174. Xu J, Hu Z, Xu Z et al (2009) Functional variant in microRNA-196a2 contributes to the susceptibility of congenital heart disease in a Chinese population. Hum Mutat 30:1231–1236