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Chromatin remodelling and epigenetic state regulation by non-coding RNAs in the diseased heart

F. De Majo, M. Calore*

Department of Cardiology, CARIM School for Cardiovascular Diseases, Maastricht University, 6229 ER Maastricht, The Netherlands

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ABSTRACT

Epigenetics refers to all the changes in phenotype and gene expression which are not due to alterations in the DNA sequence. These mechanisms have a pivotal role not only in the development but also in the maintenance during adulthood of a physiological phenotype of the heart. Because of the crucial role of epigenetic modifications, their alteration can lead to the arise of pathological conditions.

Heart failure affects an estimated 23 million people worldwide and leads to substantial numbers of hospitalizations and health care costs: ischemic heart disease, hypertension, rheumatic fever and other valve diseases, cardiomyopathy, cardiopulmonary disease, congenital heart disease and other factors may all lead to heart failure, either alone or in concert with other risk factors. Epigenetic alterations have recently been included among these risk factors as they can affect gene expression in response to external stimuli.

In this review, we provide an overview of all the major classes of chromatin remodellers, providing examples of how their disregulation in the adult heart alters specific gene programs with subsequent development of major cardiomyopathies. Understanding the functional significance of the different epigenetic marks as points of genetic control may be useful for developing promising future therapeutic tools.

1. Introduction

Originally, the term “epigenetics” was used to refer to all molecular pathways modulating the expression of a genotype into a particular phenotype [1]. Over the following years, with the rapid growth of genetics, the meaning of the word has gradually narrowed and today it stands for all the heritable alterations, such as changes in DNA conformation, transcription, or translation, that are not due to changes in DNA sequence [1]. Epigenetic events are critical to regulate the condensation state of chromatin, which represents a dynamic DNA scaffold responsive to external stimuli, and hence to modulate the accessibility of the DNA by RNA polymerase, transcription factors and DNA binding molecules. Normally, DNA is tightly coiled around histones, forming the condensed eterochromatin (Fig. 1), when genes are transcriptionally inactivated, while it opens to euchromatin in order for gene expression to take place. This so-called “chromatin remodelling” can operate both at a local and at a global level: locally it can affect single gene expression, while globally it can change the accessibility of chromosome domains or even entire chromosomes. In eukaryotes, the fundamental unit of chromosome folding is named nucleosome: it is formed by a segment of DNA about 146 bp long wrapped around eight histone proteins (Fig. 1) [2]. The DNA fragment of the nucleosome cannot be reached by the transcriptional machinery. The regulation of the accessibility of larger chromosome domains appears to involve the assembly of higher order supranucleosomal structures [2]. Chromatin remodelling is orchestrated by multiple epigenetic processes: some directly modify the DNA molecule itself (*e.g.,* DNA methylation), while others relate to modifications of chromatin associated proteins (*e.g.*, post-translational histone modification), or involve RNA molecules (*e.g.*, gene silencing by noncoding RNAs [ncRNAs]) [3,4] (Fig. 1). Epigenetic modifications can be induced by external stimuli, such as prenatal malnutrition, cigarette smoke and ultraviolet radiation, and are at the same time stable and reversible, thus accounting for the heritability and adaptation to the environment of cellular gene expression programs in the presence of a common genetic make-

* Corresponding author.
E-mail address: m.calore@maastrichtuniversity.nl (M. Calore).

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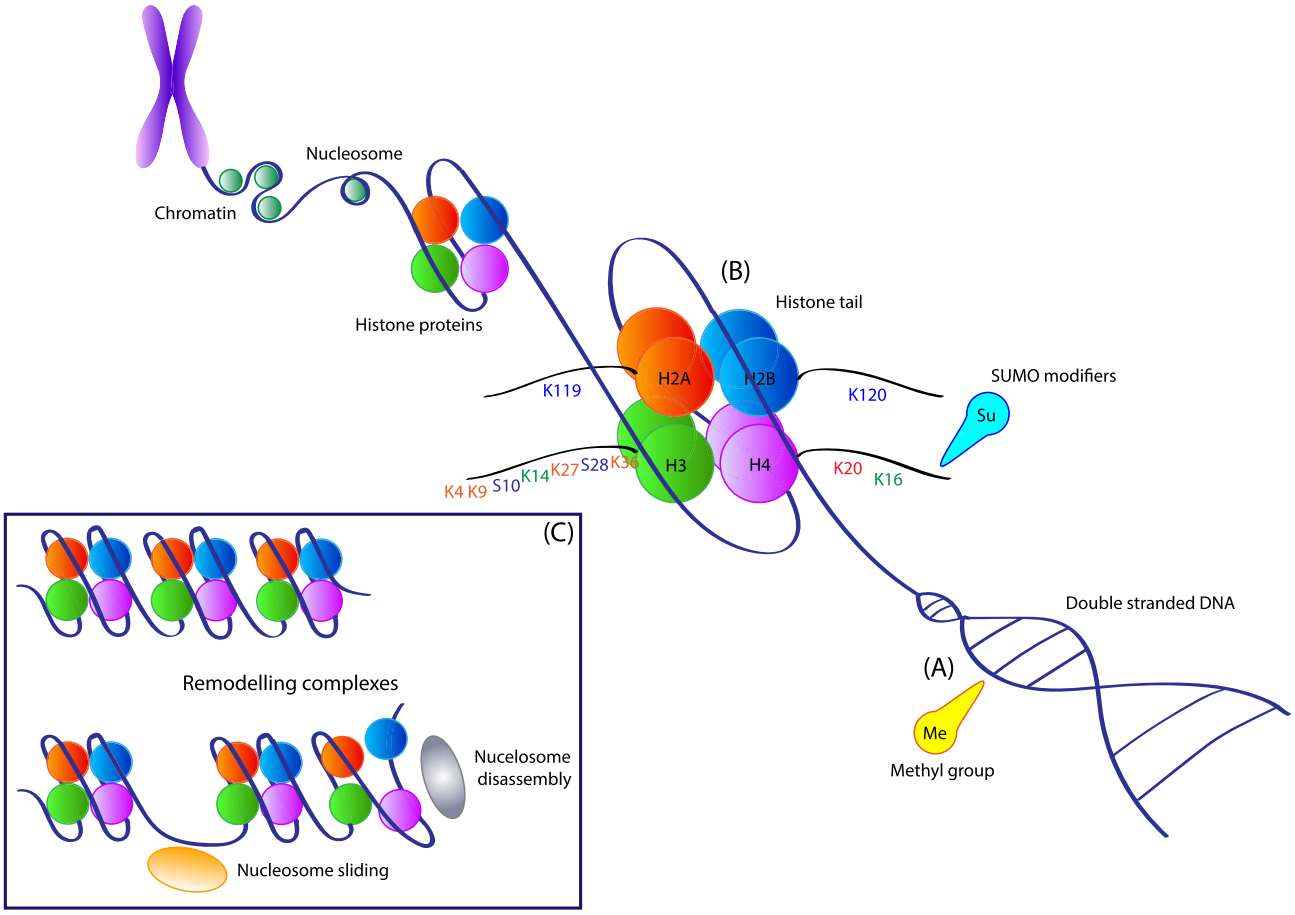

Fig. 1. Epigenetic regulation results in gene expression without involving variations in the DNA sequence itself; epigenetic mechanisms include chemical modifications of the DNA (DNA methylation) and of the histones and non-coding RNAs. (A) DNA methylation occurs predominantly at the CpG islands. (B) Histone complexes can be modified, such as by the addition of methyl- and acetyl-groups, by ubiquitination or SUMOylation, at multiple positions on the tail. The major modification positions are reported: red-methylation, dark blue-phosphorylation, green-acetylation, blue-ubiquitination. (C) Histone-remodelling complexes slide or displace histones, modifying DNA accessibility.

up. These features highlight the important role of epigenetic modifications in the modulation of cell ability to answer pathophysiological stimuli.

Heart failure (HF) is the endpoint of a myriad of cardiovascular diseases, such as myocardial infarction, hypertension, inherited cardiomyopathies, and myocarditis, which have multiple established genetic and environmental risk factors [5]. However, these factors explain only a portion of the total HF risk. Increasing evidence shed new light on epigenetic modifications as the effectors of the environmental influences in gene expression in heart development as well as cardiac diseases susceptibility (Fig. 2) [5]. It is clear that proliferative capability of cardiac cells relies on a tight epigenetic regulation that modulates the adaptation of the functionality of cardiomyocytes, fibroblasts, endothelial cells, and progenitor cells to environmental challenges and to biochemical stimuli. For instance, the work of Gilsbach et al. shows that epigenetic modifications, such as DNA methylations, are involved in cell type specification during embryonic development, as 79,655 differentially methylated regions (DMRs) have been identified when comparing adult healthy cardiomyocytes and undifferentiated ES cells: of these, 90% were hypomethylated and 10% were hypermethylated in cardiomyocytes versus ES cells [6]. The crucial role played by epigenetic processes in heart development is the reason why an impaired formation may occur if they are altered. As an example, brahma-related gene 1 (BRG1)/brahma (BRM)-associated-factor (BAF) complex, a switching defective/sucrose non-fermenting complexes (SWI/SNF) type of ATP-dependent chromatin-remodelling complex, regulates heart muscle and chamber development by interacting with transcription factors and other chromatin regulators. An early deletion of Brg1 in the developing myocardium leads to severe defects in heart growth that are associated with disruption of the expression of important regulators of heart formation, while a slightly later deletion leads to thin myocardium and absence of interventricular septum. Brg1 controls cell proliferation through Bmp10, so the lack of Brg1 affects in a negative way the level of Bmp10 too: this causes failure of myocardial cell proliferation due to the unregulated expression of $p57^{kip2}$, a cyclin-dependent kinase inhibitor that prevents cell cycle progression and that is normally silenced by Bmp10 [7, 8, 9].

Perturbations in the epigenetic regulation and subsequently in the gene expression might also result in progenitor cell dysfunction, worsening of the endogenous repair system, as well as in cardiomyocytes loss, hypertrophic response and increased extracellular matrix deposition (fibrosis), thus leading to an higher propensity for arrhythmias [10, 11]. In this review, we provide a translational overview of epigenetic regulation, from basic concepts to its relevance to cardiovascular diseases.

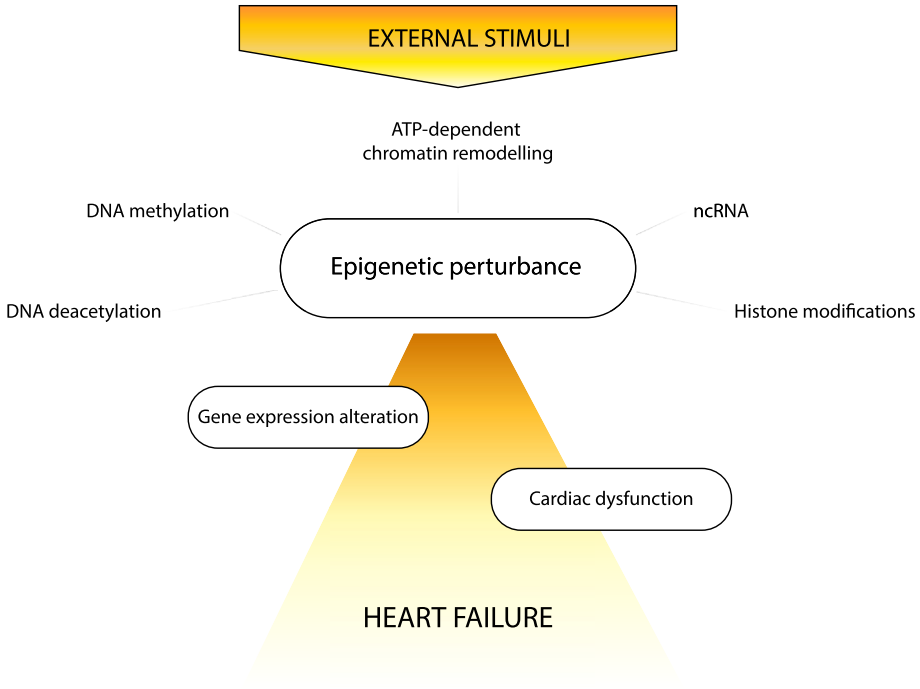

Fig. 2. Scheme representing the principal epigenetic regulations in heart failure development.

2. Chromatin remodelling in heart failure

2.1. DNA methylation

DNA methylation is the most common epigenetic chromatin modification, consisting in the covalent attachment of a methyl group to the C5 position of cytosines in the cytosine-paired-with-guanine (CpG) dimers. DNA methylation mostly occurs in promoter regions and results in epigenetic silencing [12] by protruding into the major DNA groove and so decreasing the accessibility of chromatin and inhibiting the binding of transcription factors required for gene expression [13]. DNA methyltransferases (DNMTs) are the enzymes catalysing this reaction. In mammals, three different DNMTs are known: DNMT1, DNMT3A and DNMT3B, of which only DNMT1, together with the DNA methyl-binding domain UHRF1, maintains the methylation state during the replication, while DNMT3A and DNMT3B are responsible for the *de novo* DNA methylation [14, 15]. Like all other epigenetic states, DNA methylation profiles may vary over an individual's lifetime and are influenced by environmental factors. Only recently, methylation patterns have been studied in the context of HF. In a series of studies, Movassagh et al. showed the correlation of changes in DNA methylation profiles and the gene expression of angiogenic factors, such as *PECAM1*, *ARH-GAP24* and *AMOTL2* in left ventricular samples of patients who underwent HF [16]. Moreover, genome-wide maps of DNA methylation and methylated-H3 enrichment in human cardiomyopathic hearts showed differential DNA methylation profiles in the CpG islands in the promoters and gene bodies between end-stage diseased hearts and controls, with a decreased methylation in genes upregulated in cardiomyopathies [17]. DNA methylation profiling was also studied in dilated cardiomyopathy, leading to the identification of 20 genes differentially methylated in 40 affected patients [18]. For instance, by performing a DNA methylation microarray analysis of the myocardium of patients with idiopathic dilated cardiomyopathy, altered DNA methylation patterns were found to cause abnormal expression of LY75 (encoding lymphocyte antigen 75) and ADORA2A (encoding adenosine receptor A2a) [18]. Other studies in animal models provided further information in the role of methylation in HF: nicotinic stimulation of acetylcholine receptors in mice resulted in hypermethylation of the promoters of *Tbx5* and *Gata4* leading to the downregulation of these genes and the inhibition of myocardial differentiation [19]. Moreover, increased methylation was associated with heart hypertrophy and reduced global cardiac contractility in the rat model [20]. Also, ablation of DNMT3A and DNMT3B, required for *de novo* methylation, influenced transcriptional responses, but not the phenotype of transverse aortic constriction (TAC)-induced left ventricular pressure overload mice, suggesting that *de novo* methylation in cardiomyocytes might not be essential in this pathogenic cardiac response [21].

2.2. Histone modifications

Histone proteins (H1, H2A, H2B, H3 and H4) represent the major organizational and regulatory core of chromatin. DNA is wrapped around histone octamers, consisting in a pair each of histones H2A, H2B, H3 and H4, to form the nucleosome, while histone H1 facilitates internucleosomal organization [22] (Fig. 1). Despite histones were initially believed to have only a structural role in chromatin packaging, it is now clear that post-translational modifications to these proteins constitute a distinct level of gene regulation [23]. These modifications usually occur on amino-terminal histone tails and consist of dynamic reversible processes, such as methylation, acetylation, SUMOylation, ubiquitination, ADP ribosylation, proline isomerization, phosphorylation [13], citrullination [24] and lysine-addiction of acyl groups [25] (Fig. 1). Altogether, histone modifications orchestrate the affinity for chromatin-associated proteins, which in turn regulate dynamic transitions between transcriptionally active or transcriptionally silent chromatin states [26].

One of the most studied histone tail modification is the addition or the removal of acetyl groups, respectively catalysed by histone acetyltransferase (HATs) and histone deacetylases (HDACs). Acetylated lysine residues were first discovered in histones regulating gene transcription, which is the reason why the enzymes catalysing

lysine acetylation were termed HATs: this modification, which pertains to the ε-amino group of lysines, is tightly regulated. Lysine acetylation status can be modified by HDACs: in humans, there are 18 HDAC enzymes that have been traditionally divided into separate categories called classes based on sequence similarities. Class I proteins (HDAC1, HDAC2, HDAC3, and HDAC8) have sequence similarity to the yeast Rpd3 protein, Class II proteins (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10) have sequence similarity to the yeast Hda1 protein, Class III proteins (SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7) are similar to the yeast Sir2 protein, and Class IV protein (HDAC11) shares sequence similarities with both Class I and II proteins [27, 28]. Typically, both acetylation and methylation involve lysine residues, but, while acetylation results in gene activation, the influence of histone methylation relies on the number of added methyl groups and on the interested residue. Histone methylation is ruled by the activity of histone lysine methyltransferases (KMTs) and histone lysine demethylases (KDMs); so far, 33 KMTs and 21 KDMs have been identified in human [29]. Despite the name, these enzymes can act not only on lysine but also on arginine residues and both can be mono-, di-, and trimethylated, or both monomethylated and symmetrically or asymmetrically dimethylated, respectively [30, 31]. The high number of numerous lysine and arginine residues on the histone tails, in combination with the various methylation levels that can be generated at each of these sites, provides an extremely wide regulatory potential for chromatin modifications. Increased histone dimethylation is associated with cardiac hypertrophy and failure, in combination with increased levels of atrial natriuretic peptide and brain natriuretic peptide in the left ventricle. Moreover, differential trimethylation of H3K4 and H3K9 is associated with decreased levels of *Kcnip2* and subsequent impaired sodium and L-type calcium current, prolonged duration of action potential and heart failure [32]. Furthermore, reduced methylation in histone H3 lysine 4 results in deletion of PTIP protein and increase of cardiomyocytes sensitivity to premature ventricular complexes [33]. Increased histone methylation was associated with an augmented HDAC activity, elevated levels of HMT G9a protein as well as decreased expression of sirtuin-1, a histone/protein deacetylase, decreased ventricular function and increased apoptosis in a caveolin knockout mouse model for ischemia/reperfusion [34].

Histone modifications have been investigated in several studies conducted using animal models: for instance, in the study of [35] cardiac hypertrophy induced in mice and rats by Angiotensin II injection or by aortic banding was significantly reduced by simultaneously administration of HDAC inhibitors. Finally, the study of [36] demonstrated that transcriptional reprogramming of Atp2a2 (encoding for sarcoplasmic reticulum Ca^{2+}ATPase) and Myh7 (encoding for β-myosin-heavy chain) genes, whose expression levels are considered a hallmark of pathological hypertrophy and HF, in the TAC mouse model are associated with significant changes in the methylation status of chromatin, modifying its dynamics at the promoter regions of these crucial genes.

2.3. ATP-dependent enzymes in chromatin remodelling

Among the modulators of chromatin architecture, ATP-dependent enzymes in chromatin remodelling complexes use the energy of ATP hydrolysis to change the nucleosome position in the chromosomal DNA packaging [37]. Four different families of ATP-dependent chromatin remodelling complexes have been described so far: SWI/SNF, imitation switch complexes (ISWI), chromodomain–helicase–DNA-binding complexes (CHD) and inositol-requiring 80 (INO80) complexes [38, 39]. All members of each family show peculiar DNA-histone contacts domains for chromatin remodelling, thereby addressing specific cellular need by precisely regulating gene expression [40].

SWI/SNF is one of the major regulators of gene expression: it acts by shifting and exposing DNA segments within the promoter. In mammals, the complex consists of 9–12 elements, including the core component encoded by either BRM or BRG1 [39]. While normally silenced in adult heart, BRG1 is expressed at the embryonic stage, when it interacts with poly (ADP-ribose) polymerases (PARPs) to activate the fetal gene beta-myosin heavy chain (β-MHC), while it represses alpha-myosin heavy chain (α-MHC) by interacting with HDACs. Moreover, depletion of BRG1 results in a thin, compact myocardium which, together with the absence of the interventricular septum, results in embryonic lethality. On the other hand, in the adult heart, BRG1 is reactivated in stress conditions and it interacts with HDACs and PARPs to repress α-MHC and activate β-MHC expression [9]. Moreover, it has been shown that the inducible deletion of the SWI/SNF ATPases BRG1 and BRM results in early altered metabolism, increased mitochondrial biogenesis and mitophagy, alteration in mitochondrial fusion and fission, as well as reduction in mitochondria number and size, eventually leading to HF [41].

In a study focused on the mechanistic interactions between enzymatic chromatin modifications and the ATP-dependent chromatin remodellers influencing the nucleosome position, Han et al. detected the involvement of BRG1, the histone methyl-transferase G9a/Glp and the DNA methyl transferase Dnmt3 in cardiac pathological stress in mice [42]. Once activated by stress, Brg1 orchestrates the epigenetic control by recruiting G9a and Dnmt3 to catalyse the chromatin methylation on Myh6 promoter, resulting in the silencing of the gene and in impaired cardiac contraction [42].

Another element of the SWI/SNF complex is DPF3, a transcription regulator that binds acetylated histones enabling a regulatory switch between poised and activated chromatin stages [43]. DPF3 was found upregulated in both patients with Tetralogy of Fallot, characterised by right ventricular hypertrophy and structural cardiac defects, and in a knockdown zebrafish model showing impaired cardiac muscle development and reduced ventricular contractility [44, 45]. DPF3 is expressed in two isoforms: DPF3a and DPF3b. The isoform DPF3a is phosphorylated at serine 348 upon hypertrophic stimuli and has been found upregulated in the heart of patients with aortic stenosis or hypertrophic cardiomyopathy [46]. Following the interaction between BRG1 and the activated DFP3a, the transcriptional repressor HEY is released from the DNA and the transcription of the downstream targets NPPA and GATA4 is stimulated, which in turn results in pathological cardiac hypertrophy [46].

The imitation switch complexes (ISWI) consists of two to four subunits, including one or two ATPase subunits, SNF2H or SNF2L. SNF2H and SNF2L are expressed in a tissue-specific manner and, since they can be associate with different proteins, they are able to generate different ISWI complexes [38]. Among these, the ISWI ATPase SNF2H is part of the Williams syndrome transcription factor (WSTF), a multifaceted protein that is involved in several nuclear processes, including replication, transcription and the DNA damage response. The study of Culver-Cochran et al. shows how the loss of WSTF led to an increase of heterochromatin formation, impacting the expression of a large number of genes [47]. Interestingly, WSTF is lost in Williams-Beuren syndrome (WBS), an autosomal dominant genetic disorder that arises after the deletion of 1.5–1.8 megabases in chromosome 7q11.23. Patients affected with this syndrome experience a large variety of symptoms, including cardiac defects, cognitive impairment, hypercalcaemia, growth deficiencies and a distinct craniofacial phenotype [48]. Studies performed *in vivo* and *in vitro* pointed WSTF haploinsufficiency as a crucial contributor to this disease [49, 50].

The CHD family of ATP-dependent chromatin remodelling

enzymes comprises proteins with two tandem chromatin organization modifier (chromo) domains and two SNF2-like ATP-dependent helicase domains. The chromodomains contain methyl-binding cages that facilitate the binding to methylated histone residues, while the helicase-ATPase domains function by promoting mechanical disruption of DNA-histone contacts. Consequently, the core histones either slide along the DNA template or are evacuated and deposited onto another DNA strand [51].

CHD proteins as epigenetic factors have been implicated in the maintenance, survival and proliferation of stem cell populations and in directing cell fate determination as well as embryonic development. Mutations such as heterozygous loss-of-function mutations in the gene encoding CHD7 have been associated to the CHARGE syndrome, a sporadic autosomal-dominant genetic disorder characterized by a variety of birth defects including atrioventricular septal abnormalities [52] In mice, the homozygous null mutations in *cdh7* lead embryonic lethality, while heterozygous mutants are viable and show many features of CHARGE syndrome, including heart defects, choanal atresia, postnatal growth retardation, genital abnormalities, abnormal semicircular canals and cleft palate [53, 54].

The inositol-requiring 80 (INO80) complex was first isolated from the yeast *Saccharomyces cerevisiae* by Ebbert et al., who suggested a possible role as chromatin remodeller [55]. Later, Shen et al. defined INO80 subunit composition and demonstrated its function in chromatin remodelling as catalyser of ATP-dependent nucleosome sliding *in vitro* [56]. The human INO80 shows some structural differences from the one described in yeast, such as a set of metazoan-specific subunits in addition to the Ino80 ATPase and other core subunits, including the Gli-Kruppel zinc finger transcription factor Yin-Yang 1 (YY1), the deubiquitylating enzyme Uch37 and nuclear factor related to κB (NFRKB) [57]. So far, evidences of a pathological effect of the loss of function of INO80 in the heart have not been broadly reported. Only the alteration of INO80 function caused by a genetic defect of YY1AP1, one of the components of this complex, has been recently associated to the occurrence of the fibromuscular dysplasia (FMD), an heterogeneous group of non-atherosclerotic and non-inflammatory arterial diseases, that are part of the Grange Syndrome, an autosomal-recessive condition characterized by arterial occlusive disease, hypertension, congenital cardiac defects, bone fragility, brachysyndactyly, and learning disabilities [58]. The two loss-of-function variants of YY1AP1 described in this study are predicted to cause nonsense-mediated mRNA decay or to produce a 80 kDa truncated protein with 91 residues deleted. The loss of YY1AP1 leads to an increased p21/WAF/CDKN1A levels and eventually to the G1 and G2 growth arrest of the vascular smooth muscle cells [58].

2.4. ncRNAs

Only 1.2% of the human genome encodes for protein-coding exons (coding mRNA) building the basis for protein synthesis, while its majority encodes an ever-expanding array of ncRNAs, whose functions are mostly still to be deciphered [59]. According to their sizes, ncRNAs are subdivided in two main categories: small ncRNAs (<200 nucleotides long), such as micro RNAs (miRNAs), or Piwi-interacting RNAs (piRNAs) and long ncRNAs, among which are included circular RNAs (circRNAs), having a length above 200 nucleotides [4].

While ncRNAs have been consistently associated with heart pathophysiology by targeting a plethora of genes (for reviews see Ref. [4, 60, 61]) less is known about the role of these RNA species in relation to chromatin remodelling. In particular, in this context, only few studies on miRNAs and lncRNAs have been described, which are reported below.

2.4.1. miRNAs in chromatin remodelling of the diseased heart

MicroRNAs are 20–22 nucleotides long RNA sequences that originate from longer precursor RNA transcripts termed primary miRNAs: these are transcribed by RNA polymerase II (Pol II) from either the introns of protein coding genes, introns and exons of non-coding genes, or intergenic genome regions. Primary miRNAs are hundreds to thousands of nucleotides long and are cleaved to 70–100 nucleotide long hairpin-shaped precursor miRNAs by RNase III enzyme Drosha and double-stranded RNA binding protein DGCR8 in the nucleus. Pre-miRNAs are then transported from nucleus to cytoplasm by nuclear export factor exportin 5 and subsequently processed into 19–25 nucleotide long duplex miRNA–miRNA*s by RNase III enzyme Dicer. The duplex binds to the Argonaute protein, the effector of the RISC complex, leading to the unwinding of the duplex and the degradation of one of the two strands. The mature single stranded miRNA associated to RISC then binds the 3′-UTR region of specific messenger RNAs leading to their degradation, destabilization, or translational inhibition [59,60] (Fig. 3).

In 1993, the works of Lee [62] and Wightman [63] reported for the first time a miRNA, lin-14, in the nematode *Caenorhabditis elegans*; nine years later in a report of Calin [64], the pathogenic effect of miRNA-15a/miRNA-16 cluster deletion in the development of chronic leukemia was described. Since then, the involvement of miRNAs dysregulations as a cause of several other kinds of diseases was studied, including the pathogenesis of cardiac diseases. The interplay between miRNAs and epigenetic modifications in the heart has been only marginally reported. Mir-133a was shown not only to target all the three mammalian DNMTs in a model of diabetic cardiomyopathy [65], but also to be regulated by HDACs [66]. Studies on CD1 mice which underwent transverse aortic constriction (TAC) coupled with *in vitro* assays performed on samples of these same mice showed that treatment with class I and IIb HDAC inhibitor led to miR-133a upregulation together with the parallel improvement of cardiac function and the attenuation of cardiac remodelling. This suggests that HDACs regulates miR-133a expression during pressure overload hypertrophy [66]. Moreover, the upregulation of the miR-212/132 cluster was observed in mouse hearts after TAC or after activation of α1 and β1-adrenoreceptors and resulted in the repression of the methyl-CpG-binding protein 1 (MeCP2), a member of the methylated DNA–binding domain protein family, which specifically binds methylated DNA sequences [67, 68]. MeCP2 repression was associated with an improvement of the diseased phenotype, consisting in pathological hypertrophy as well as contractile and mitochondrial dysfunction. These results highlight the importance of the adrenergic activation of the microRNA-MeCP2 epigenetic pathway in cardiac adaptation in the development and the recovery from HF [69]. These reports underline the complexity of the network between miRNAs and epigenetic pathways to form an epigenetic–miRNA regulatory circuit involved in a different level of gene expression regulation. Additional studies are required to further clarify how epigenetic events impact miRNAs important in HF as well as how miRNAs may impact the epigenetic marks of genes associated with HF.

2.4.2. lncRNAs in chromatin remodelling of the diseased heart

lncRNAs are transcripts >200 nucleotides long that have no known protein-coding function. However, this definition may be preliminary, since many lncRNAs have been recently reported to encode short peptides in human tissues [70]. LncRNAs may include antisense, intronic and intergenic transcripts, in addition to enhancer elements, pseudogenes, and retrotransposon transposable element transcripts; they can also be natural antisense transcripts (from the opposite DNA strand of protein or not protein-coding genes), 3′ UTR-associated transcripts of mRNA or

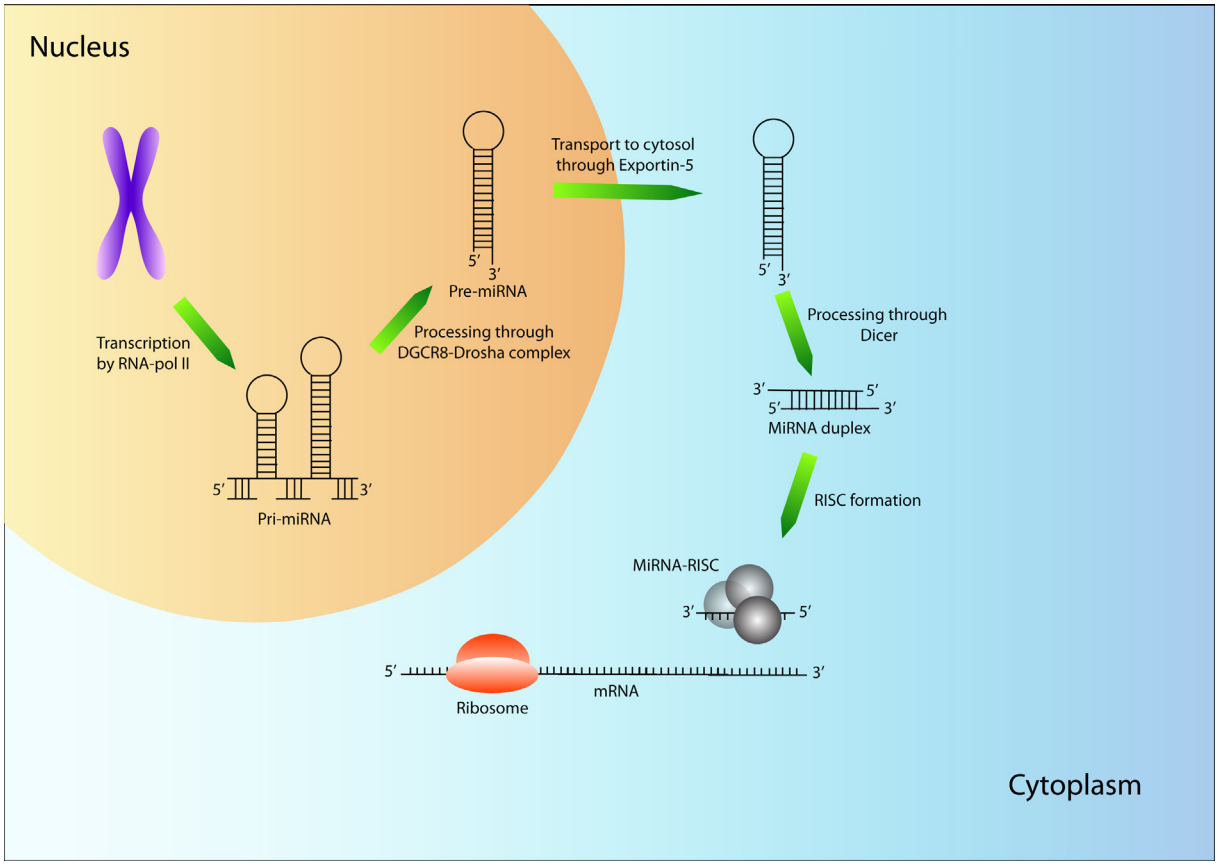

Fig. 3. miRNAs biogenesis and function.

ultraconserved element RNAs [59]. LncRNAs are transcribed by the same transcriptional machinery as protein coding RNAs and may undergo alternative splicing and so generating a wide variety of isoforms. LncRNAs can also rapidly shift between different stable 3-dimensional conformations, facilitating rapidly adaptable conformation-dependent “signalling switches” [59]. [4,70, 71] The implication of lncRNAs in several biological processes arises from their ability to interact with a wide variety of macromolecules present within the cell, including other RNA species, such as mRNAs, miRNAs, but also other lncRNAs, proteins and DNA [70]. Within the processes in which lncRNAs are involved, the chromatin remodelling in the pathogenesis of cardiac diseases has been reported too.

The Myosin Heavy-chain-associated RNA Transcript (Mhrt) was found downregulated in conditions of pressure overload resulting in hypertrophy and HF [4,72]. Interestingly, it was shown to antagonize the function of Brg1, which is, as already mentioned, a stress-activated ATP- dependent chromatin-remodelling factor implicated in the regulation of pathological gene expression (see above): by binding to the helicase domain of Brg1, Mhrt interferes with its binding to the DNA targets, preventing the expression of stress-induced genes [4, 72]. Another example is the lateral mesoderm-specific lncRNA Fendrr, a lncRNA found to regulate heart and body wall development in mouse [73]. Fendrr loss in mice embryos results in a drastic reduction of the histone-modifying complex PRC2 and of H3K27 trimethylation as well as in the increase of H3K4 trimethylation. Mechanistically, it turned out that Fendrr exerts its function by directly binding the PRC2 and TrxG/MLL complexes, suggesting a role in modulating chromatin signature in the heart [73]. Moreover, Braveheart (Bvht) was shown to have a role in the establishment of the cardiac lineage in mice [74]. In particular, Bvht was demonstrated to interact with SUZ12, a component of PCR2, during cardiac differentiation in mouse, which is suggestive of a role of this lncRNA in gene expression regulation through chromatin remodelling [74]. Also, the Cardiac Hypertrophy Associated Epigenetic Regulator (*Chaer*), a lncRNA required for the development of cardiac hypertrophy, was reported to interact with PRC2 [75]. In this case, the interaction with the complex occurs through a 66-mer motif and results in the inhibition of histone H3 lysine23 methylation of hypertrophic associated genes. Interestingly, the interaction is induced by mTORC1 and the inhibition of *Chaer* in healthy hearts prior the induction of pressure overload results in reduction of cardiac dysfunction [75]. Another lncRNA implicated in cardiac hypertrophy is Cardiac Hypertrophy Associated Transcript *(Chast)*, found to be upregulated in hypertrophic mice hearts after transaortic constriction-induced pathological cardiac remodelling. The human homolog CHAST has been also reported to be upregulated in the heart tissue of aortic stenosis patients as well as in ES cell derived cardiomyocytes after hypertrophic stimulation [76]. In the study of Micheletti et al. another lncRNA named *Wisper* has been found to correlate to cardiac fibrosis following myocardial infarction in a murine model: 14 days after MI induced by left anterior descending artery (LAD) ligation, it results maximally expressed, thus suggesting its involvement in the cardiac fibrosis driving pathological remodelling [77]. Further experiments validated this overexpression in activated fibroblasts of infarcted hearts. Accordingly, the human horthologue of this lncRNA, WISPER, has been also implied in the cardiac fibrosis in heart tissue from human patients suffering from aortic stenosis [77]. The Cardiac Apoptosis-Related LncRNA (CARL) has been

implicated in the regulation of mitochondrial apoptotic pathway in cardiomyocytes: in both human subjects and experimental models of HF, mitochondrial function is decreased, thus suggesting a link between mitochondrial integrity and cardiac pathophysiology [78]. [79] In the study of Wang et al., *Carl* has been found to act as an endogenous sponge for miR-539, known to affect mitochondrial apoptotic pathway through targeting PHB2 transcript, leading to increased mitochondrial fission and apoptosis [80]. An alteration of this pathway may contribute to a worsening of the consequences of MI, as suggested by the evidence that an enforced expression of PHB2 results in a reduction in mitochondrial fission, apoptosis and infarct sizes in an ischemia/reperfusion model [80].

Evidences from genome-wide studies demonstrated that enhancers can be transcribed to produce enhancer-derived lncRNAs named eRNAs [81]. eRNAs are generated from genomic regions with high H3K4me1-to-me3 ratio of histone methylation, and usually don't display polyadenylation or splicing, but exhibit transcription rates comparable to lncRNAs or coding mRNAs, thus producing less stable transcripts [81]. The (CAR)diac (M)esoderm (E)nhancer-associated (N)oncoding RNA, CARMEN is an example of eRNA involved in cardiac specification and differentiation: it regulates the cardiac gene network during cardiomyocytes differentiation by interacting with SUZ12 and EZH2, both components of PRC2 [82]. Interestingly, the same study also shown that CARMEN silencing can also block Bvht induction, that, as discussed above, is another lncRNA implicated in cardiac development. Moreover, CARMEN expression level results increased in response to cardiac stress in murine models of MI. It is notewhorthy that human CARMEN isoforms are also induced in idiopathic dilated cardiomyopathy (DCM) and aortic stenosis patients [82].

Circular RNAs (circRNAs) are a class of lncRNAs characterized by the presence of a covalent linkage at the ends of the RNA molecule that leads to the formation of a circular structure. CircRNAs were discovered in plants and shown to encode subviral agents [59]; in unicellular organisms, they mostly stem from self-splicing introns of pre-ribosomal RNA, but can also arise from protein-coding genes in archaea [59]. In mammals, circRNAs were initially thought to be a very narrow class of ncRNAs but they actually turned out to be a growing group of post-transcriptional regulators: their feature is to act as miRNAs sponges by binding miRNAs thus preventing their interaction with their targets [83]. The first circRNA described to be functional in the heart is the so-called heart-related circRNA (HRCR). HRCR is normally present in mouse hearts but its expression decreases in hypertrophic and failing hearts [83]. Interestingly, HRCR binds and sequesters miR-223, a miRNA that causes cardiac hypertrophy via inhibition of the apoptosis inhibitor with CARD domain protein ARC [84]. CDR1AS is a circRNA targeting miR-7 which is induced after acute MI in mice and resulted to be pro-apoptotic *in vitro*, which is consistent with the anti-apoptotic role of miR-7 [83]. Accordingly, CDR1AS overexpression results in larger infarct sizes after acute MI, which prevented by the simultaneous overexpression of miR-7 [83]. Despite a large number of circRNAs are known to be involved in heart diseases, their function in the heart is only known in few cases. A remarkably large number of circRNAs are produced from the titin gene (TTN), that is known to undergo highly complex alternative splicing [85]. The RNA-binding motif protein 20 (RBM20) is involved in the splicing of TTN gene and, as reported in the study of Khan et al., it is also fundamental for the generation of a number of circRNAs deriving from it [86]. Accordingly, in the Rbm20-null mouse model, which manifests left ventricular dilatation and impaired cardiac function, some circRNAs derived from the titin gene are absent [86].

2.4.3. Other ncRNAs in chromatin remodelling of the diseased heart

PIWI-interacting RNAs (piRNAs) are RNA molecules 26–31 nucleotides long originally regarded as ncRNAs involved in the maintenance of genome integrity by modulating the expression of retrotransposons [87-90]; more recent evidences indicate that piRNAs have also other functions, such as the regulation of mRNAs expression. An example is the one reported in the studies of Vella et al. and Rajan et al., which highlight how piRNAs may also act by influencing the AKT signalling pathway, a crucial network in heart physiopathology. This evidence suggests that piRNAs could play a functional role in cardiomyocyte proliferation and regeneration [91]. [92].

Small Nucleolar RNAs (snoRNAs) are single-stranded RNA molecules 60–300 nucleotides long and in mammals more than 90% of them are encoded within introns. Their main function is the targeting of ribosomal RNAs and spliceosomal RNAs for biochemical modification [59]. The study of O'Brien et al. suggests that snoRNAs may be involved in the regulation of the expression of genes implicated in cardiac development [93]. The expression levels of snoRNAs in heart samples of infants affected with tetralogy of Fallot (TOF) not only resulted to differ from the healthy condition for several snoRNAs but also that was surprisingly similar to the fetal expression pattern [93]. In addition, in myocardium from children with TOF, in the 51% of genes critical for cardiac development splicing variants were found; since snoRNAs can target spliceosomal RNAs, this finding suggests a link between the altered levels of snoRNAs and the defects in heart development of TOF infants [93].

3. Conclusions

Genes are firmly packed in chromatin, which represents a dynamic DNA scaffold responsive to external stimuli. Changes in chromatin state are reversible and are able to coordinate gene expression. The whole variety of mechanisms involved in the regulation of chromatin condensation status are part of epigenetics. These processes have a pivotal role in the proper development of the heart as well as in the maintenance of the correct cardiac function in the adult, while alterations in these events have been observed in different cardiovascular diseases, as broadly discussed in this review. Further studies are required to define an exhaustive profiling of epigenetic changes in cardiovascular pathophysiology, with the potential of providing a renewable benefit in different sectors. More focus should be given to the understanding of the chromatin modifications regulating cardiac gene function in physiological and pathological settings. Indeed, the identification of the disease-specific epigenetic factors-target gene axis could help clarifying the pathogenic events resulting in adverse cardiac phenotypes. Consequently, this will enable the development of new therapeutic strategies for cardiovascular diseases targeting proteins involved in newly discovered pathways. In parallel, also the epigenetic factors could represent a novel therapeutic target. In this context, different examples have been reported of how inhibition of mediators of chromatin remodelling, as DNMTs or HDACs, can affect in a positive or negative way the phenotype of different disease models: though, the drawback in the use of epigenetic treatments affecting DNA or histone acetylation/methylation states is that of possible off-target effects. This problem may be overcome by focusing instead on ncRNAs contribution to chromatin remodelling: ncRNAs action is more tissue specific than the one of the other epigenetic machineries that tend to operate widely in many tissues, thus lowering the risk of unwanted outcomes of the treatment. Moreover, tools for the therapeutic manipulation of ncRNAs are already available, like siRNA interfering, antisense oligonucleotides, aptamers, ribozymes, or CRISPR/Cas techniques. These interventions have a strong potential in providing a novel personalised tool to prevent or treat HF development.

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References

[1] G. Felsenfeld, A brief history of epigenetics, Cold Spring Harbor Perspect. Biol. 6 (1) (2014).
[2] S.I.S. Grewal, D. Moazed, Heterochromatin and Epigenetic Control of gene expression, Science 301 (5634) (2003) 798–802.
[3] S.R. Martinez, M.S. Gay, L. Zhang, Epigenetic mechanisms in heart development and disease, Drug Discov. Today 20 (7) (2015) 799–811.
[4] T. Thum, G. Condorelli, Long noncoding RNAs and microRNAs in cardiovascular pathophysiology, Circ. Res. 116 (4) (2015) 751–762.
[5] S. Khatibzadeh, F. Farzadfar, J. Oliver, M. Ezzati, A. Moran, Worldwide risk factors for heart failure: a systematic review and pooled analysis, Int. J. Cardiol. 168 (2) (2013) 1186–1194.
[6] R. Gilsbach, S. Preissl, B.A. Gruning, T. Schnick, L. Burger, V. Benes, et al., Dynamic DNA methylation orchestrates cardiomyocyte development, maturation and disease, Nat. Commun. 5 (2014) 5288.
[7] J.K. Takeuchi, X. Lou, J.M. Alexander, H. Sugizaki, P. Delgado-Olguin, A.K. Holloway, et al., Chromatin remodelling complex dosage modulates transcription factor function in heart development, Nat. Commun. 2 (2011) 187.
[8] C.P. Chang, B.G. Bruneau, Epigenetics and cardiovascular development, Annu. Rev. Physiol. 74 (2012) 41–68.
[9] C.T. Hang, J. Yang, P. Han, H.L. Cheng, C. Shang, E. Ashley, et al., Chromatin regulation by Brg1 underlies heart muscle development and disease, Nature 466 (7302) (2010) 62–67.
[10] C. Schiano, M.T. Vietri, V. Grimaldi, A. Picascia, M.R. De Pascale, C. Napoli, Epigenetic-related therapeutic challenges in cardiovascular disease, Trends Pharmacol. Sci. 36 (4) (2015) 226–235.
[11] A. Berezin, Epigenetics in heart failure phenotypes, BBA clinical 6 (2016) 31–37.
[12] P.A. Jones, D. Takai, The role of DNA methylation in mammalian epigenetics, Science 293 (5532) (2001) 1068–1070.
[13] D.E. Handy, R. Castro, J. Loscalzo, Epigenetic modifications: basic mechanisms and role in cardiovascular disease, Circulation 123 (19) (2011) 2145–2156.
[14] G. Auclair, M. Weber, Mechanisms of DNA methylation and demethylation in mammals, Biochimie 94 (11) (2012) 2202–2211.
[15] S. Guibert, M. Weber, Functions of DNA methylation and hydroxymethylation in mammalian development, Curr. Top. Dev. Biol. 104 (2013) 47–83.
[16] M. Movassagh, M.K. Choy, M. Goddard, M.R. Bennett, T.A. Down, R.S. Foo, Differential DNA methylation correlates with differential expression of angiogenic factors in human heart failure, PLoS One 5 (1) (2010) e8564.
[17] M. Movassagh, M.K. Choy, D.A. Knowles, L. Cordeddu, S. Haider, T. Down, et al., Distinct epigenomic features in end-stage failing human hearts, Circulation 124 (22) (2011) 2411–2422.
[18] J. Haas, K.S. Frese, Y.J. Park, A. Keller, B. Vogel, A.M. Lindroth, et al., Alterations in cardiac DNA methylation in human dilated cardiomyopathy, EMBO Mol. Med. 5 (3) (2013) 413–429.
[19] X.Y. Jiang, Y.L. Feng, L.T. Ye, X.H. Li, J. Feng, M.Z. Zhang, et al., Inhibition of Gata4 and Tbx5 by nicotine-mediated DNA methylation in myocardial differentiation, Stem Cell Rep. 8 (2) (2017) 290–304.
[20] D. Xiao, C. Dasgupta, M. Chen, K. Zhang, J. Buchholz, Z. Xu, et al., Inhibition of DNA methylation reverses norepinephrine-induced cardiac hypertrophy in rats, Cardiovasc. Res. 101 (3) (2014) 373–382.
[21] T.G. Nührenberg, N. Hammann, T. Schnick, S. Preißl, A. Witten, M. Stoll, et al., Cardiac myocyte de novo DNA methyltransferases 3a/3b are dispensable for cardiac function and remodeling after chronic pressure overload in mice, PLoS One 10 (6) (2015) e0131019.
[22] K. Luger, A.W. Mader, R.K. Richmond, D.F. Sargent, T.J. Richmond, Crystal structure of the nucleosome core particle at 2.8 A resolution, Nature 389 (6648) (1997) 251–260.
[23] B.D. Strahl, C.D. Allis, The language of covalent histone modifications, Nature 403 (6765) (2000) 41–45.
[24] M.A. Christophorou, G. Castelo-Branco, R.P. Halley-Stott, C.S. Oliveira, R. Loos, A. Radzisheuskaya, et al., Citrullination regulates pluripotency and histone H1 binding to chromatin, Nature 507 (7490) (2014) 104–108.
[25] S. Rousseaux, S. Khochbin, Histone acylation beyond acetylation: terra incognita in chromatin biology, Cell J. 17 (1) (2015) 1–6.
[26] T. Jenuwein, C.D. Allis, Translating the histone code, Science 293 (5532) (2001) 1074–1080.
[27] E. Seto, M. Yoshida, Erasers of histone acetylation: the histone deacetylase enzymes, Cold Spring Harbor Perspect. Biol. 6 (4) (2014) a018713.
[28] A. Drazic, L.M. Myklebust, R. Ree, T. Arnesen, The world of protein acetylation, Biochim. Biophys. Acta 1864 (10) (2016) 1372–1401.
[29] T. Zhang, S. Cooper, N. Brockdorff, The interplay of histone modifications - writers that read, EMBO Rep. 16 (11) (2015) 1467–1481.
[30] A.J. Bannister, T. Kouzarides, Histone methylation: recognizing the methyl mark, Meth. Enzymol. 376 (2003) 269–288. Academic Press.
[31] M.T. Bedford, S. Richard, Arginine methylation an emerging regulator of protein function, Mol. Cell 18 (3) (2005) 263–272.
[32] R. Kaneda, S. Takada, Y. Yamashita, Y.L. Choi, M. Nonaka-Sarukawa, M. Soda, et al., Genome-wide histone methylation profile for heart failure, Gene Cell. Devoted Mol. Cell. Mech. 14 (1) (2009) 69–77.
[33] A.B. Stein, T.A. Jones, T.J. Herron, S.R. Patel, S.M. Day, S.F. Noujaim, et al., Loss of H3K4 methylation destabilizes gene expression patterns and physiological functions in adult murine cardiomyocytes, J. Clin. Invest. 121 (7) (2011) 2641–2650.
[34] Y.M. Tsutsumi, Y.T. Horikawa, M.M. Jennings, M.W. Kidd, I.R. Niesman, U. Yokoyama, et al., Cardiac-specific overexpression of caveolin-3 induces endogenous cardiac protection by mimicking ischemic preconditioning, Circulation 118 (19) (2008) 1979–1988.
[35] H.J. Kee, I.S. Sohn, K.I. Nam, J.E. Park, Y.R. Qian, Z. Yin, et al., Inhibition of histone deacetylation blocks cardiac hypertrophy induced by angiotensin II infusion and aortic banding, Circulation 113 (1) (2006) 51–59.
[36] T. Angrisano, G.G. Schiattarella, S. Keller, G. Pironti, E. Florio, F. Magliulo, et al., Epigenetic switch at atp2a2 and myh7 gene promoters in pressure overload-induced heart failure, PLoS One 9 (9) (2014) e106024.
[37] C.R. Clapier, B.R. Cairns, The biology of chromatin remodeling complexes, Annu. Rev. Biochem. 78 (2009) 273–304.
[38] M. Lange, S. Demajo, P. Jain, L. Di Croce, Combinatorial assembly and function of chromatin regulatory complexes, Epigenomics 3 (5) (2011) 567–580.
[39] L. Ho, G.R. Crabtree, Chromatin remodelling during development, Nature 463 (7280) (2010) 474–484.
[40] J. Newell-Price, A.J. Clark, P. King, DNA methylation and silencing of gene expression, Trends Endocrinol. Metabol. TEM (Trends Endocrinol. Metab.) 11 (4) (2000) 142–148.
[41] S.J. Bultman, D. Holley, G. de Ridder, S. Pizzo, T.N. Sidorova, K.T. Murray, et al., BRG1 and BRM SWI/SNF ATPases redundantly maintain cardiomyocyte homeostasis by regulating cardiomyocyte mitophagy and mitochondrial dynamics in vivo, Cardiovasc. Pathol. Offic. J. Soc. Cardiovasc. Pathol. 25 (3) (2016) 258–269.
[42] P. Han, W. Li, J. Yang, C. Shang, C.H. Lin, W. Cheng, et al., Epigenetic response to environmental stress: assembly of BRG1-G9a/GLP-DNMT3 repressive chromatin complex on Myh6 promoter in pathologically stressed hearts, Biochim. Biophys. Acta 1863 (7 Pt B) (2016) 1772–1781.
[43] L. Zeng, Q. Zhang, S. Li, A.N. Plotnikov, M.J. Walsh, M.M. Zhou, Mechanism and regulation of acetylated histone binding by the tandem PHD finger of DPF3b, Nature 466 (7303) (2010) 258–262.
[44] B. Kaynak, A. von Heydebreck, S. Mebus, D. Seelow, S. Hennig, J. Vogel, et al., Genome-wide array analysis of normal and malformed human hearts, Circulation 107 (19) (2003) 2467–2474.
[45] M. Lange, B. Kaynak, U.B. Forster, M. Tönjes, J.J. Fischer, C. Grimm, et al., Regulation of muscle development by DPF3, a novel histone acetylation and methylation reader of the BAF chromatin remodeling complex, Genes Dev. 22 (17) (2008) 2370–2384.
[46] H. Cui, J. Schlesinger, S. Schoenhals, M. Tonjes, I. Dunkel, D. Meierhofer, et al., Phosphorylation of the chromatin remodeling factor DPF3a induces cardiac hypertrophy through releasing HEY repressors from DNA, Nucleic Acids Res. 44 (6) (2016) 2538–2553.
[47] A.E. Culver-Cochran, B.P. Chadwick, Loss of WSTF results in spontaneous fluctuations of heterochromatin formation and resolution, combined with substantial changes to gene expression, BMC Genom. 14 (2013) 740.
[48] C.A. Morris, S.A. Demsey, C.O. Leonard, C. Dilts, B.L. Blackburn, Natural history of Williams syndrome: physical characteristics, J. Pediatr. 113 (2) (1988) 318–326.
[49] L. Bozhenok, P.A. Wade, P. Varga-Weisz, WSTF-ISWI chromatin remodeling complex targets heterochromatic replication foci, EMBO J. 21 (9) (2002) 2231–2241.
[50] R. Cus, D. Maurus, M. Kuhl, Cloning and developmental expression of WSTF during Xenopus laevis embryogenesis, Gene Expr. Patterns GEP 6 (4) (2006) 340–346.
[51] A. Joseph, Micucci EDSaDMM. Chromodomain helicase DNA-binding proteins in stem cells and human developmental diseases, Stem Cell. Dev. 24 (8) (2015).
[52] S.A. Balow, L.X. Pierce, G.E. Zentner, P.A. Conrad, S. Davis, H.E. Sabaawy, et al., Knockdown of fbxl10/kdm2bb rescues chd7 morphant phenotype in a zebrafish model of CHARGE syndrome, Dev. Biol. 382 (1) (2013) 57–69.
[53] E.A. Hurd, P.L. Capers, M.N. Blauwkamp, M.E. Adams, Y. Raphael, H.K. Poucher, et al., Loss of Chd7 function in gene-trapped reporter mice is embryonic lethal and associated with severe defects in multiple developing tissues, Mamm. Genome Offic. J. Int. Mammalian Genome Soc. 18 (2) (2007) 94–104.
[54] E.A. Bosman, A.C. Penn, J.C. Ambrose, R. Kettleborough, D.L. Stemple, K.P. Steel, Multiple mutations in mouse Chd7 provide models for CHARGE syndrome, Hum. Mol. Genet. 14 (22) (2005) 3463–3476.
[55] R. Ebbert, A. Birkmann, H.J. Schuller, The product of the SNF2/SWI2 paralogue INO80 of Saccharomyces cerevisiae required for efficient expression of various yeast structural genes is part of a high-molecular-weight protein complex, Mol. Microbiol. 32 (4) (1999) 741–751.

[56] X. Shen, G. Mizuguchi, A. Hamiche, C. Wu, A chromatin remodelling complex involved in transcription and DNA processing, Nature 406 (6795) (2000) 541–544.
[57] R.C. Conaway, J.W. Conaway, The INO80 chromatin remodeling complex in transcription, replication and repair, Trends Biochem. Sci. 34 (2) (2009) 71–77.
[58] D.C. Guo, X.Y. Duan, E.S. Regalado, L. Mellor-Crummey, C.S. Kwartler, D. Kim, et al., Loss-of-Function mutations in YY1AP1 lead to Grange syndrome and a fibromuscular dysplasia-like vascular disease, Am. J. Hum. Genet. 100 (1) (2017) 21–30.
[59] T.G. Di Salvo, Epigenetic regulation in heart failure: Part I RNA, Cardiol. Rev. 23 (5) (2015) 213–228.
[60] G. Condorelli, M.V. Latronico, E. Cavarretta, microRNAs in cardiovascular diseases: current knowledge and the road ahead, J. Am. Coll. Cardiol. 63 (21) (2014) 2177–2187.
[61] P.A. Da Costa Martins, L.J. De Windt, MicroRNAs in control of cardiac hypertrophy, Cardiovasc. Res. 93 (4) (2012) 563–572.
[62] R.C. Lee, R.L. Feinbaum, V. Ambros, C. The, Elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14, Cell 75 (5) (1993) 843–854.
[63] B. Wightman, I. Ha, G. Ruvkun, Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans, Cell 75 (5) (1993) 855–862.
[64] G.A. Calin, C.D. Dumitru, M. Shimizu, R. Bichi, S. Zupo, E. Noch, et al., Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia, Proc. Natl. Acad. Sci. U.S.A. 99 (24) (2002) 15524–15529.
[65] V. Chavali, S.C. Tyagi, P.K. Mishra, MicroRNA-133a regulates DNA methylation in diabetic cardiomyocytes, Biochem. Biophys. Res. Commun. 425 (3) (2012) 668–672.
[66] L. Renaud, L.G. Harris, S.K. Mani, H. Kasiganesan, J.C. Chou, C.F. Baicu, et al., HDACs regulate miR-133a expression in pressure overload-induced cardiac fibrosis, Circ. Heart Fail. 8 (6) (2015) 1094–1104.
[67] J. Guy, H. Cheval, J. Selfridge, A. Bird, The role of MeCP2 in the brain, Annu. Rev. Cell Dev. Biol. 27 (2011) 631–652.
[68] T. Baubec, R. Ivánek, F. Lienert, D. Schübeler, Methylation-dependent and -independent genomic targeting principles of the MBD protein family, Cell 153 (2) (2013) 480–492.
[69] S.C. Mayer, R. Gilsbach, S. Preissl, E.B. Monroy Ordonez, T. Schnick, N. Beetz, et al., Adrenergic repression of the epigenetic reader MeCP2 facilitates cardiac adaptation in chronic heart failure, Circ. Res. 117 (7) (2015) 622–633.
[70] T. Thum, Facts and updates about cardiovascular non-coding RNAs in heart failure, Esc Heart Fail. 2 (3) (2015) 108–111.
[71] C. Liang Joe, J. Bloom Ryan, D. Smolke Christina, Engineering biological systems with synthetic RNA molecules, Mol. Cell 43 (6) (2011) 915–926.
[72] P. Han, W. Li, C.H. Lin, J. Yang, C. Shang, S.T. Nuernberg, et al., A long noncoding RNA protects the heart from pathological hypertrophy, Nature 514 (7520) (2014) 102–106.
[73] P. Grote, L. Wittler, D. Hendrix, F. Koch, S. Wahrisch, A. Beisaw, et al., The tissue-specific lncRNA Fendrr is an essential regulator of heart and body wall development in the mouse, Dev. Cell 24 (2) (2013) 206–214.
[74] C.A. Klattenhoff, J.C. Scheuermann, L.E. Surface, R.K. Bradley, P.A. Fields, M.L. Steinhauser, et al., Braveheart, a long noncoding RNA required for cardiovascular lineage commitment, Cell 152 (3) (2013) 570–583.
[75] Z. Wang, X.J. Zhang, Y.X. Ji, P. Zhang, K.Q. Deng, J. Gong, et al., The long noncoding RNA Chaer defines an epigenetic checkpoint in cardiac hypertrophy, Nat. Med. 22 (10) (2016) 1131–1139.
[76] J. Viereck, R. Kumarswamy, A. Foinquinos, K. Xiao, P. Avramopoulos, M. Kunz, et al., Long noncoding RNA Chast promotes cardiac remodeling, Sci. Transl. Med. 8 (326) (2016) 326 ra22.
[77] R. Micheletti, I. Plaisance, B.J. Abraham, A. Sarre, C.-C. Ting, M. Alexanian, et al., The long noncoding RNA Wisper controls cardiac fibrosis and remodeling, Sci. Transl. Med. (395) (2017) 9 eaai9118.
[78] M.G. Rosca, E.J. Vazquez, J. Kerner, W. Parland, M.P. Chandler, W. Stanley, et al., Cardiac mitochondria in heart failure: decrease in respirasomes and oxidative phosphorylation, Cardiovasc. Res. 80 (1) (2008) 30–39.
[79] V.G. Sharov, A.V. Todor, N. Silverman, S. Goldstein, H.N. Sabbah, Abnormal mitochondrial respiration in failed human myocardium, J. Mol. Cell. Cardiol. 32 (12) (2000) 2361–2367.
[80] K. Wang, B. Long, L.Y. Zhou, F. Liu, Q.Y. Zhou, C.Y. Liu, et al., CARL lncRNA inhibits anoxia-induced mitochondrial fission and apoptosis in cardiomyocytes by impairing miR-539-dependent PHB2 downregulation, Nat. Commun. 5 (2014) 3596.
[81] T.K. Kim, M. Hemberg, J.M. Gray, A.M. Costa, D.M. Bear, J. Wu, et al., Widespread transcription at neuronal activity-regulated enhancers, Nature 465 (7295) (2010) 182–187.
[82] S. Ounzain, R. Micheletti, C. Arnan, I. Plaisance, D. Cecchi, B. Schroen, et al., CARMEN, a human super enhancer-associated long noncoding RNA controlling cardiac specification, differentiation and homeostasis, J. Mol. Cell. Cardiol. 89 (2015) 98–112.
[83] Y. Devaux, E.E. Creemers, R.A. Boon, S. Werfel, T. Thum, S. Engelhardt, et al., Circular RNAs in heart failure, Eur. J. Heart Fail. 19 (6) (2017) 701–709.
[84] K. Wang, B. Long, F. Liu, J.X. Wang, C.Y. Liu, B. Zhao, et al., A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223, Eur. Heart J. 37 (33) (2016) 2602–2611.
[85] W. Guo, S. Schafer, M.L. Greaser, M.H. Radke, M. Liss, T. Govindarajan, et al., RBM20, a gene for hereditary cardiomyopathy, regulates titin splicing, Nat. Med. 18 (2012) 766–773.
[86] M.A. Khan, Y.J. Reckman, S. Aufiero, M.M. van den Hoogenhof, I. van der Made, A. Beqqali, et al., RBM20 regulates circular RNA production from the titin gene, Circ. Res. 119 (9) (2016) 996–1003.
[87] A. Aravin, D. Gaidatzis, S. Pfeffer, M. Lagos-Quintana, P. Landgraf, N. Iovino, et al., A novel class of small RNAs bind to MILI protein in mouse testes, Nature 442 (7099) (2006) 203–207.
[88] J. Brennecke, A.A. Aravin, A. Stark, M. Dus, M. Kellis, R. Sachidanandam, et al., Discrete small RNA-generating loci as master regulators of transposon activity in Drosophila, Cell 128 (6) (2007) 1089–1103.
[89] A. Girard, R. Sachidanandam, G.J. Hannon, M.A. Carmell, A germline-specific class of small RNAs binds mammalian Piwi proteins, Nature 442 (7099) (2006) 199–202.
[90] M. Moyano, G. Stefani, piRNA involvement in genome stability and human cancer, J. Hematol. Oncol. 8 (1) (2015) 38.
[91] S. Vella, A. Gallo, A. Lo Nigro, D. Galvagno, G.M. Raffa, M. Pilato, et al., PIWI-interacting RNA (piRNA) signatures in human cardiac progenitor cells, Int. J. Biochem. Cell Biol. 76 (2016) 1–11.
[92] K.S. Rajan, G. Velmurugan, G. Pandi, S. Ramasamy, miRNA and piRNA mediated Akt pathway in heart: antisense expands to survive, Int. J. Biochem. Cell Biol. 55 (2014) 153–156.
[93] J.E. O'Brien, N. Kibiryeva, X.-G. Zhou, J.A. Marshall, G.K. Lofland, M. Artman, et al., Noncoding RNA expression in myocardium from infants with tetralogy of Fallot clinical perspective, Circ.Cardiovasc. Genet. 5 (3) (2012) 279–286.