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Transcription Factor Expression Regulation Mechanisms and It's Role in Cardiovascular Diseases

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Abstract

Complex multicellular organisms are composed of different tissues whose individual characteristics depend on the specific proteins expressed selectively and differentially by their cell types. These proteins can function as structural cell components, regulatory enzymes of metabolism, transcription factors, cellular receptors and intracellular signaling components. The incorrect expression of such proteins, their expression in the wrong places at the wrong time, or the production of specific proteins or proteins of anomalous function in abnormal amounts underlies all cellular pathology with a genetic basis. Therefore, knowledge on regulation mechanisms of protein expression in eukaryotes will contribute to the understanding of the molecular basis of various pathologies.

The mechanisms of regulation of gene expression operate at the following different levels: transcriptional control, post-transcriptional control (Processing and Transport of Primary RNA), translational or protein synthesis control, and post-translational control. The different control mechanisms include the specific sequences in DNA, the existence of enzymes and regulatory proteins (Recognition Factors) and the chemical modification of DNA, RNA and proteins. Specifically, in heart and cardiac cells have described epigenetic mechanisms and networks of transcription factors essential for their differentiation, but the epigenome remodeling of these differentiated terminal cells during fetal development, postnatal maturation and cardiovascular diseases is unknown. The present review article aimed to provide an overview of the mechanisms of gene regulation in eukaryotic cells and to show that each of these mechanisms is crucial for the maintenance of cell integrity

Keywords: Cardiovascular Diseases; Gene Expression; Transcription Factors; Transcriptional Regulation; Translational Regulation

Abbreviations

TF	:	Transcription Factors
C/EBP	:	CCAAT-Box /Enhancer/Binding/Protein
Enhancer	:	Regulatory-Enhancing Sequences
ZIP	:	Leucine Zipper
HLH	:	Helix Loop Helix
PABP	:	Poly A Binding Protein
ASF	:	Alternative Splicing Factors
SRC-1	:	Steroid Receptor Coactivator 1
GRIP-1	:	Glucocorticoid Receptor Interacting Protein 1
NcoA-1	:	Nuclear Hormone Receptor Coactivator 1
TF	:	Transcription Factors
CTF	:	CCAAT Box-Binding Transcription Factor
PTGS	:	Post-Transcriptional Gene Silencing
HDAC	:	Histone Deacetylases
HAT	:	Histone Acetyltransferase
RISC	:	RNA-Induced Silencing Complex
siRNA	:	Small Interfering RNA

miRNA	:	Micro-Rna
lncRNAs	:	Long Noncoding Rnas
Dnmt	:	DNA Methyltransferase
SUMO	:	Small Ubiquitin-L Modifier
MEF2	:	Enhancer Factor of Myocytes 2
GSK3β	:	Glycogen Synthase Kinase 3 Beta

Introduction

In eukaryotic cells, the ability to express biologically active proteins results from different regulatory levels. Genetic regulation is defined as the processes that affect the action of the gene at the level of transcription or translation or after these processes are completed. In these processes, the functional products of a gene are regulated, allowing a cell to control a structure and function. The mechanisms of regulation of gene expression operate at different levels as follows: transcriptional control, post-transcriptional control (Processing and Transport of Primary RNA), translational control or protein synthesis, and post-translational control. The different control mechanisms include specific sequences in DNA, the existence of enzymes and regulatory proteins (recognition factors) and the chemical modification of DNA, RNA and proteins [1,2].

Regulation Levels of Gene Expression in Eukaryotes

DNA conformation and structure

Chromatin differential compaction affects the binding capacity of enzymes and transcriptional factors of specific genes. Chromatin can be divided into two types according to its staining pattern as follows: euchromatin stains smoothly and corresponds to genome regions available for transcription, whereas heterochromatin or dense chromatin is intensely stained and corresponds to genome regions that are densely compacted and inaccessible to the transcriptional apparatus. There are two types of heterochromatin: constitutive, which refers to chromosomes or part of them that are heterochromatic in all cells of the same species; and facultative, which involves chromosome zones that can de-compact in euchromatin in some cells of the same organism. Because heterochromatin cannot be transcribed, gene expression in eukaryotes can be repressed by euchromatin condensation in heterochromatin. All the factors that modulate chromatin decompaction are not yet known [3-5].

Histone acetylation and deacetylation are frequent covalent modifications in these chromatin decompaction phenomena. For example, acetylation of coactivators is involved in genetic transcripts modulated by thyroid hormones. Acetylation occurs in the lysine residues of the N-terminal tails of histones, reducing their positive charge and thus their binding affinity to negatively charged DNA. Histone deacetylation, mediated by deacetylases, causes the opposite effect (Re-Compaction) [6-8].

DNA Covalent Modifications

Methylation of Deoxycytidine Residues

Deoxycytidine residues occur in specifically recognized sequences (5'-mCpG-3') that are usually grouped into GC-abundant "islands" within or near regulatory transcription regions. CpG islands are sequences of approximately 1 kb whose abundance in the CpG islands is greater than in the rest of the genome. Genes are expressed strongly when CpG islands are poorly methylated (Hypomethylated), whereas they are not expressed if the CpG islands are hypermethylated [9,10]. Methylation inhibits gene transcription by interfering with the ability of transcription factors to recognize DNA-binding sites or by altering DNA conformations, making polymerization of the RNA polymerase difficult. Methylation of cytosine residues in DNA, especially at the promoter sites, makes transcription difficult. In mammals, methylated DNA forms heterochromatin, which is inaccessible for transcription factors. Therefore, methylated genes cannot be transcribed even residually, thereby becoming an efficient mechanism of gene silencing that decreases the amount of DNA that transcription factors and RNA polymerase must trace to search for promoters [4,9,11-13].

Modification of gene number and structure

The total or partial elimination of genes prevents the formation of mRNA and the corresponding protein. The presence of tandem genes implies the multiple copies of a gene, which increase the production capacity of the required protein in large quantities as occurs in genes encoding histones and 5S RNA. Gene regulation is also performed according to the availability of DNA by increasing the number of copies of an accessible gene [14]. This mechanism is known as gene amplification, which is the successive repetition of the replication of a specific DNA sequence. This phenomenon is observed in the amplification of certain genes whose products are necessary for the development of some insects and amphibians, such as ribosomal RNA in *Xenopus laevis*, in which genes encoding 5.8S, 18S and 28S RNA are amplified from 500 to 2 million copies.

Proteins that modulate transcription

In eukaryotes, both RNA molecules and proteins can act as regulators. Among the proteins, some are part of the holoenzyme polymerase, and others are involved in the remodeling of chromatin. Moreover, a third group of proteins binds DNA to regulate transcription.

Transcriptional activators: Transcriptional activators are proteins that bind to distal elements (SDE and Enhancers) to activate transcription. These activators are specific to a few promoters (will not be in all cell types), recognize between 6 and 14 bp in the promoter and usually present the following two structural domains: DNA-binding domain, which consists of 60 to 100 consecutive amino acids; and the activation domain of the transcript, which consists of 30 to 100 amino acids that are not consecutive and that are classified into three main types. The three main activation

domain types are as follows: Gln-rich domain, as the SP1 factor that binds to GC boxes; Pro-rich domain, as the CTF factor that binds to CAAT boxes; and the Gal4p and Gnc4p acid-rich domain (Yeast Activators), which loses activating capacity when the acidic residue is removed but gains activating capacity when the basic residue is mutated. The presence of these domains converts them into modular proteins, in which the binding domain and the activation domain can function independently [3,15,16].

Coactivators and corepressors: The action of a transcription activator (or a repressor) can be exerted directly on the basal complex either on the RNA polymerase (one of the TFII or TAFII) or through an intermediary molecule, which can be a coactivator or a corepressor. A coactivator contributes to activate transcription, and a single coactivator can receive signals from different activators to transmit them towards the basal promoter complex. The coactivators formed by a single polypeptide chain include the p160 family, such as steroid receptor coactivator 1 (SRC-1), glucocorticoid receptor interacting protein 1 (GRIP-1) and nuclear hormone receptor coactivator 1 (NcoA-1). The coactivators formed by several polypeptides include the mediator (MED), TRAP/SMCC, PC2, DRIP, CRSP, NAT or ARC. In contrast, a corepressor contributes to inactivate the promoter [3,17].

Transcriptional control of gene expression: The transcriptional control of gene expression includes promoters, enhancing regulatory sequences (Enhancers), and the interaction between multiple activating or inhibiting proteins that act by binding to specific DNA recognition sequences. The regulations can be of the "CIS" or "TRANS" type. CIS regulation is determined when the transcriptional regulatory element is part of the polynucleotide chain where the gene to be regulated is located. When the regulatory elements are of a different nature and origin than the genetic sequence to be controlled, the regulation is of the TRANS type [18].

CIS regulation promoters

The initial step of the synthesis of the three types of RNA is the location of the RNA polymerases next to a DNA sequence at the level of the gene promoter to be transcribed. The most complex of regulatory processes is that which comprises class II genes or mRNA encoders. Almost all protein coding genes contain two types of basal promoters and a varying number of transcriptional regulatory domains. The most frequent promoters are those of the CCAAT and TATA types, which are known as motifs or boxes because of their high evolutionary conservation. The TATA box is located 20-30 bp upstream of the transcription start site. Numerous proteins identified as TFIIA, TFIIB, and TFIIC (Regulatory Factors of RNA Polymerase II) interact with the TATA box. The CCAAT promoter resides 50-130 bp upstream of the transcriptional start site, and C/EBP (CCAAT-box /enhancer/binding/protein) binds to this sequence [18]. Another regulatory sequence includes the GC box. Although promoters are preferably located upstream (5') of the transcriptional start, some can be located downstream (3') or are intragenic. The number and type of regulatory elements vary according to each mRNA. The nature of the promoters and the combination of the proteins that interact with them are part of the main regulatory mechanisms in inducible genes [15].

Regulatory-enhancing sequences (Enhancers): DNA sequences can be located upstream or downstream of the gene thousands of base pairs from the promoter. DNA regions in which activating actions are exerted are called enhancers or augmentations. In general, a regulator sequence or enhancer regulates the frequency with which the transcriptional process is performed. There are also regulators of opposite action (Silencers or Transcription Dampers). The simplest explanation of the regulatory phenomenon at a distance proposes that the DNA molecule is doubled in a loop to allow the approach of these areas distant from the double helix and locates the activator protein linked to the enhancer [3,19,20]

TRANS regulation - Transcription factors

Within the transcriptional regulation are Transcription Factors (TF), which are responsible for performing transcription preferentially. TFs are nuclear localization proteins that bind to specific DNA sequences and that modulate gene expression to participate in the regulation of DNA transcription but without being part of the RNA polymerase. TFs can act by recognizing and binding to specific DNA sequences, joining other factors, or joining directly to the RNA polymerase. When activated, TFs acquire the ability to regulate gene expression in the cell nucleus either by activating or repressing the transcription of various genes [3,21].

In contrast to bacterial RNA polymerases, eukaryotic RNA polymerases do not directly contact the DNA promoter but instead are recruited towards the promoter by specific protein complexes for each type of RNA polymerase. These complexes are called SL1, TFIID and TFIIIB for RNA polymerase I, RNA pol II, and RNA pol III, respectively. There are also general TFs, which are components of the basal transcription complex, and tissue-specific TFs, which bind to specific promoter/regulatory regions of genes and regulate the level of transcription from the basal transcription complex [3,21].

In addition to the DNA binding-domain, TFs may possess dimerization domains for the non-covalent, reversible interaction of one protein with another. The interaction of two proteins through these domains may be a requirement for their binding to DNA. Therefore, the union of regulatory factors is often cooperative. While multiple dimeric factors possess two proteins of the same species (Homodimers), others are formed by two proteins of different nature (Heterodimers). In addition to dimerization domains, this type of protein possesses DNA-binding domains and transcriptional activation domains [3].

According to its structure, different TF families have been defined

Zinc fingers

DNA-binding structures that require zinc for their binding activity, and these motifs consist of specific spacings formed by cysteine

and histidine residues that allow the binding of Zn^{2+} cations to the protein, producing a coordinative link of the metal in the center of them. This motif has a finger-like appearance for which it is commonly known as the "zinc finger" [22]. This type of protein is usually organized in a series of 9 repeated domains, containing 30 amino acids folded in a simple structural unit around a zinc atom to which the cysteine and histidine are attached in varying numbers, resulting in different families. These families include the cys-cys-his-his (2 Cysteines and 2 Histidines), cys-cys-cys-cys (4 Cysteines), and cys-cys-his-cys (3 Cysteines and 1 Histidine) families [22-24]. The most typical examples include the TF of RNA polymerase II (TFIIIA) and the superfamily protein receptors of permissive hormones (Steroids and Thyroid). Other TFs that present zinc fingers are GATA proteins, which are important in normal cardiac development [25], as well as the MAZ protein, which is crucial in the genetic expression control of the CD4 cell surface glycoprotein [22,24,26].

Leucine zipper (ZIP)

The ZIP is a motif that is caused by the repetitive distribution of leucine residues spaced by seven amino acids in an alpha helical distribution of the protein [22,27], and this domain is preceded by a zone of basic amino acids. ZIPs allow binding to specific recognition sequences of DNA in the form of dimers in areas near the promoters and activating or enhancer regions of the genes. Along with additional factors, ZIPs contribute to the efficiency with which RNA polymerase binds to the promoter and initiates transcription. In general, all these proteins activate transcription in a constitutive or regulated manner through post-translational modification (usually by phosphorylation) in response to external stimuli. Multiple b-Zip factors are expressed specifically in different cell types or in a regulated manner depending on the development patterns, and they contribute to tissue differentiation [24,28,29]. ZIP domains are present in proteins such as c-myc, c-fos, c-jun and C/EBP [22].

Helix-Loop-Helix (HLH)

The HLH domain consists of two alpha-helix regions separated by a region of varying lengths that forms a loop between them. Alpha-helix domains are structurally similar and necessary for interaction with protein sequences that allow symmetric conformation in relation to an axis; as in leucine zipper domains, this structural class presents a basic region that is in contact with DNA and possesses a dimerized region of two alpha helices [22,23]. The ZIP family and the HLH family present a subfamily of domains known as basic leucine zipper (bZIP) and basic helix-loop-helix (bHLH) [29], which are characterized by the presence of an adjacent HLH and ZIP basic domain [28]. These transcription factors regulate gene expression through their specific binding to DNA, and they bind as dimers to symmetric DNA sites [24,30]. The basic domain of these proteins controls the binding to the consensus DNA sequence of CANNTG. This consensus sequence is referred to as the E-box motif (E-box) and is present in the regulatory regions of some tissue-specific genes. Examples of this group of proteins include Myo D, c-Myc, Max, USF, AP4, TFE3 and TFEB [28,31].

Homeodomains

The DNA-binding region of 60 amino acids encoded by a 180 bp DNA sequence is known as a homeobox. Homeodomains are necessary both for early cell lineage decisions, such as the formation of the basic body plan of vertebrates, and for late decisions, such as differentiation and organogenesis [32-35]. Homeodomains have diverged greatly throughout evolution in eukaryotes, but they all contain highly conserved residues that may be necessary for DNA binding [36].

Post-Transcriptional Control of Gene Expression

Although the initiation of transcription is the primary regulation site of gene expression, the synthesis of the primary transcript is not the only time that cells control the adequate production of proteins.

Alternative Polyadenylation Sites

Something like the alternative sites of transcription initiation may occur but at the 3' end. In this case, several sites capable of being polyadenylated, such as the gene for the immunoglobulin m heavy chain, are found on the same gene. Depending on the 3' polyadenylated site, the resulting protein can be anchored to the membrane or be secreted according to the developmental stage of the cell [3,37,38].

Alternative Splicing

Alternative splicing is a mechanism that allows a single gene to code for more than one protein. In multiple cases, more than one route is known to process the primary transcript, obtaining structurally and functionally different proteins or isoforms of a protein. The cuts on the hnRNA must be produced with absolute precision. Splicing may occur when one or more exons are removed (Producing A Shorter Protein) or when one or more introns are not removed (Producing A Longer Protein). A family of six proteins known as alternative splicing factors (ASFs) is responsible for recognizing and selecting the places for alternative cuts. ASFs contain domains rich in serine and arginine (also known as SR proteins). The mechanism by which the cell selects the sites is unclear. Some genes coding for transcription factors in cells in developmental stages can be assembled alternatively, and the production of one or another variant will determine the differentiation path adopted by the cell. In most cases, the difference between alternative splicing products on a single RNA differs in key regions, which may affect the following protein properties: compartmentalization, type of ligand to which it will bind, binding affinity, and catalytic activity if it is an enzyme [3,39-41].

RNA editing (Directed RNA Mutagenesis): Alternative splicing is the best studied and most usual way of regulating gene expression at the level of RNA processing, but it is not the only one. A point mutation of a base in mRNA or hnRNA can alter the product. A point mutation is not an error, but it is a tool used by

the cell to achieve a certain protein. In humans, this is the case of apoproteins B100 and B48. Both are encoded by the same gene and contain the same exons and introns in hnRNA. When the gene is expressed in hepatocytes, the hnRNA does not undergo any modification, and the processed mRNA is translated into ApoB100. When the gene is expressed in enterocytes, however, a point mutation is produced that converts C residues to U residues in the mRNA, configuring a stop codon that codes for ApoB48 [3,42].

Stability of mRNA: Contrary to prokaryotic mRNA, in which the half-life is approximately 1-5 minutes, the stability of eukaryotic mRNA varies widely. The length of the poly A tail is directly related to the cytosolic stability of the mRNA, which is associated with the protection exerted by this sequence when competing with the rest of the chain for binding to cytosolic nucleases. The poly A tail is linked to a protein known as poly A binding protein (PABP), which protects the sequence from the action of general nucleases and sensitizes it to a poly A-specific nucleases. As these nucleases act, the poly A tail is shortened until it can no longer bind to PABP, and the mRNA becomes susceptible to general nucleases and is rapidly degraded. Certain unstable transcripts possess predominant sequences, but not exclusively, in the 3' regions that constitute signals of rapid degradation for cytoplasmic nucleases. These sequences are known as destabilizing sequences, which consist of approximately 50 nucleotides and are rich in A and U residues. A group of, cytoplasmic nucleases, known as ribozymes that possess a small RNA in their active site specifically pair with these 3'end sequences, accelerating the degradation of mRNA [3,42,43].

Translational Control of Gene Expression

Almost one-third of cytoplasmic mRNA is not bound to ribosomes even when more than 90% of the ribosomes are active. The speed at which mRNA is translated as well as the number of times that it must be translated can be regulated. There is a general, global or nonspecific control of the translation exerted on the factors of the translation complex. Specific cases or particular control of the translation of certain mRNAs are known [15,37].

General translational control: All cellular mRNA present methylated guanosine capping, and such structure increases translation. If for some reason of spatial arrangement of the 5' end of the RNA and capping is not available for its interaction with the initiation factor eIF4E, translation is decreased. The activity of the eIF2B, eIF3, eIF4B and eIF4F initiation factors can also be controlled by phosphorylation, a mechanism that in turn responds to various stimuli that can be either be physiological (Kinase Cascade Activating Factors) Or Not (Severe Malnutrition, Hyperosmolarity, Viral Infection or Thermal Shock). For example, eIF2B is phosphorylated by a cAMP-independent protein kinase that responds to stress signals and is inactivated by preventing the formation of the 40S complex. In turn, eIF4F is phosphorylated by insulin and mitogen-activated kinase cascades, which induces the activation of the factor, promoting an increase in translation. There are two proteins (4E-BP1 and 4E-BP2) that bind and inactivate eIF4F; insulin and growth factors phosphorylate these proteins by releasing eIF4F and leaving the phosphorylation sites available to enhance the stimulation of factor activity as well as protein synthesis [3,37].

Particular translational control: Translation control depends on regulatory substances that modify the configuration of a stretch of non-translatable nucleotides located at the 5' end between the cap and the initiation codon, e.g., the translation of the ferritin messenger that binds to iron for its intracellular deposit. When cytosolic iron concentrations increase, ferritin synthesis occurs at high speeds, and iron binds to aconitase or IRF. In contrast, when these concentrations decrease, the IRF becomes free and binds to the mRNA of ferritin, forming a loop at the 5' end that prevents the binding of eIF4F and the assembly of the translation apparatus, thereby blocking unnecessary protein production [3,15,37].

Translational Frame Shift

In translation frame shifts, the ribosome shifts the reading frame at some point in its displacement along the mRNA, moving a nucleotide backward or forward, thus enabling the same messenger to produce two proteins [44].

Stop codon read through: In a stop codon read through, the ribosome jumps the stop codon and continues to read the nucleotide sequence [45].

Translational Bypassing

In translation bypassing, the ribosome ignores a nucleotide sequence in the messenger, resulting in the messenger being longer than the protein because an internal portion of the message remains untranslated, enabling a single messenger to produce two proteins [46].

Post-Translational Control of Gene Expression

The nascent peptide of the ribosome can undergo various modifications according to its subsequent biological function, including removal of the amino terminal end, export signals, acylations, methylations, sulfations, glycosylations, prenylations, vitamin C-dependent modifications, vitamin K-dependent carboxylations (such as in the case of coagulation factors) or post-translational cleavages, to become active (which is a way to control their activity as in the case of some enzymes and peptide hormones). All these modifications can be controlled by internal (e.g., Intracellular pH and Molecular Chaperone Activity) or external (kinase cascades that control phosphorylation) signals. Any problem in these post-translational modifications can trigger alterations in the physiology of the cell. Regardless of the structure and function of the protein, a correct post-translational folding of the peptides is indispensable because the formation of secondary, supra-secondary and tertiary structures as well as the oligomerizations will be responsible for making the protein functional [3,37,47].

Control Over Protein Stability

Cells can control the survival time of proteins once they

have been synthesized and modified post-translationally. Although it is not directly concerning the regulation of gene expression, it is an extension of the topic. The mechanisms that control protein stability are not well understood. However, proteins in which the amino terminals are rich in methionine, serine, alanine, threonine, valine and glycine are stable for more than 20 hours, whereas those that are rich in phenylalanine, aspartic acid, lysine and arginine are stable for less than 5 minutes. This is known as the "N-end Rule". The last mentioned sequences are known as "PEST Sequences", which are highly sensitive to ubiquitin recognition and are degraded in the proteasome [48].

Posttranslational modifications play a fundamental role in regulating the folding of proteins, their targeting to specific subcellular compartments, their interaction with ligands or other proteins, and their functional state, such as catalytic activity in the case of enzymes or the signaling function of proteins involved in signal transduction pathways. The interplay between modifying and demodifying enzymes allows for rapid and economical control of protein function. A similar control by protein degradation and de novo synthesis would take much longer time and cost much more bioenergy [49].

Phosphorylation

Phosphorylation is a strictly post-translational modification once the protein is completely synthesized and folded. Phosphorylation affects OH groups of Ser, Thr and Tyr, causing a remarkable increase of negative charge in the protein. Phosphorylation is reversible and frequent. Phosphorylation occurs via protein kinases by transferring the (γ) group of ATP, and dephosphorylation is catalyzed by protein phosphatases [15,41].

Acetylation

Acetylation is a covalent modification that introduces an acetyl group in the amino of an amino acid. Acetylation of the amino terminus Met (which deactivates the sequencing of the protein) is most frequent, but it can also occur on histone Lys to change its affinity for DNA as mentioned above [50]. Histone acetylation has been recognized as an important post-translational modification of core nucleosomal histones that changes access to the chromatin to allow gene transcription, DNA replication, and repair. Histone acetyltransferases were initially identified as co-activators that link DNA-binding transcription factors to the general transcriptional machinery. Over the years, more chromatin-binding modes have been discovered suggesting direct interaction of histone acetyltransferases and their protein complex partners with histone proteins. While much progress has been made in characterizing histone acetyltransferase complexes biochemically, cell-free activity assay results are often at odds with in-cell histone acetyltransferase activities. In-cell studies suggest specific histone lysine targets, but broad recruitment modes, apparently not relying on specific DNA sequences, but on chromatin of a specific functional state. Here we review the evidence for general versus specific roles of individual nuclear lysine acetyltransferases in light of in vivo and in vitro data in the mammalian system [51].

Hydroxylation

Hydroxylation consists of the incorporation of OH groups into Pro and Lys residues in the case of collagen. This modification is performed by several hydroxylases present in the endoplasmic reticulum. The reaction is chemically complex because it entails the decarboxylation of the OH donor molecule [15,37].

Acylation

Acylation is a co-translational modification, which consists in the union of a fatty acid to increase hydrophobicity of the protein and the lipid to anchor the membrane, generally on the inner side. Acylation generally occurs on Ser, Thr or Cys. Multiple proteins involved in signal transduction (Ser/Thr/Tyr kinases, G proteins) are myristylated, which occurs on a N-Glu-X-X-X- (Ser/Thr)–YY sequence where Y represents basic amino acids [15, 37].

Ubiquitination and Sumoylation

Multiple proteins are targeted for ubiquitination, a modification consisting of the covalent conjugation of ubiquitin, a protein of 76 amino acids (9 kDa), to a lysine residue [7,52]. Specifically, the C-terminal carboxyl group of the small ubiquitin protein is attached to the ε-amine of a lysine residue of a substrate protein through an isopeptide bond. This process has been shown to be involved in the regulation of many cellular processes including protein degradation and gene expression and dysfunction of these processes is implicated in many human diseases [53].

In general, all proteins, including histones, can be poly-ubiquitinated, which appears to be a signaling marker to degrade the protein in the proteasome. Lysine mono-ubiquitination, a modification that is not associated with the degradation of proteins, can participate in the regulation of protein activity. Certain inactive precursors of transcriptional factors of RNA-pol II, are processed in the proteasome to their active forms in a manner dependent on mono-ubiquitination, which translates into the modulation of transcription [48,52].

Sumoylation is a process similar to ubiquitination, but the conjugated protein is small ubiquitin-related modifier (SUMO), an 11 kDa protein. Histone sumoylation has been related to processes of transcriptional repression mediated by the recruitment of histone deacetylase and HP1 [54,55]. Sumoylation also participates in the attenuation of the expression of transcriptionally active genes, which will subsequently be repressed [56].

Other Post-Translational Modifications

Prenylation consists of joining terpenoid radicals (isoprene derivatives) to the Cys of the cytosolic proteins and serving as an anchor to the membrane. The most common terpenoids are geranyl (10C), farnesyl (15C) and geranylgeranyl (20C). The Ras oncoprotein must be farnesylated to be oncogenic. G-proteins and some proteins of the nuclear matrix (Laminins) are also prenylated [57].

ADP-ribosylation is a reversible modification on His, Arg, Asn, Lys or Glu residues using NAD^+ as a co-substrate.

Diphtheria, cholera and pertussis toxins nonspecifically ADP-ribosylate intracellular proteins (e.g., eIF-2), thereby disturbing cell physiology. Similarly, this activity is performed on a telomeric protein to regulate the assembly and disassembly of the telomere. In some proteins, Tyr can be sulfated in the Golgi complex [15,58,59]. This is a key process in the regulation of protein activities and thus cellular signaling pathways is the modification of proteins by post-translational mechanisms. Knowledge about the enzymes (writers and erasers) that attach and remove post-translational modifications, the targets that are modified and the functional consequences elicited by specific modifications, is crucial for understanding cell biological processes. Moreover, detailed knowledge about these mechanisms and pathways helps to elucidate the molecular causes of various diseases and in defining potential targets for therapeutic approaches [60].

Gene silencing

Gene silencing may occur by inactivation by interaction with a regulator, post-transcriptional gene silencing (PTGS, also known as co-suppression or gene extinction), and DNA methylation in vertebrates (directly linked to supercoiling and silencing as mentioned above).

Post-Transcriptional Gene Silencing (PTGS)

PTGS consists of the specific degradation of the complementary mRNA of one of the dsRNA. Degraded mRNAs are often aberrant transcripts of diverse origins. PTGS is also known as co-suppression or extinction (quelling). This aberrant RNA is the substrate of a RNA-directed RNA polymerase that generates a long molecule of dsRNA, which is known as the dsRNA trigger and is fragmented by the dicer ribonuclease into a series of dsRNA 21 to 25 nucleotides in length known as small interfering RNA (siRNA). siRNA is associated with a series of proteins to form the RNA-induced silencing complex (RISC) [61,62]. In this complex, one of the siRNA strands serves as a guide to locate any complementary mRNA present in the cell to destroy it by an endoribonuclease of the RISC complex. This mechanism is extremely conserved among eukaryotic organisms (Protozoa, Mammals, Plants, Fish, Insects, Fungi, Invertebrates and Humans). Therefore, PTGS can be a mechanism of regulation and defense, which is crucial in several cellular processes as follows: defending against the invasion of intrusive nucleic acids (Usually Viruses); integrity of the genome because it represses the transposition of mobile elements; destruction of aberrant mRNA, which would generate intracellular disorientation; and maintenance of the supercoiled areas (heterochromatin) of the genome [63]. In some organisms (for example, in human cells), PTGS manifests as a transient phenomenon (which ceases with the disappearance of the exogenous dsRNA trigger), and in others (plants and nematodes), PTGS is amplified and diffused towards the rest of the cells of the organism and can become heritable at least for some generations (in Drosophila and in nematodes, but not in plants).

Gene Expression Regulation by Means of Micro-RNA

As mentioned above, RNA silencing is initiated from dsRNA, which may have various origins. In eukaryotic organisms, some genes do not encode proteins but instead highly structured RNA with double-stranded portions, which are processed by dicer-type enzymes resulting in RNA of 21-26 nucleotides known as micro-RNA (miRNA) [64]. These miRNAs share multiple characteristics with conventional siRNA, but each precursor RNA results in a single miRNA. Each miRNA is incorporated into a RISC complex where it induces its action. The miRNA presents complementary sequences to that of messenger RNA from different genes and can promote the cutting of target RNA or inhibition of its translation depending on the degree of complementarity (Hutvágner). In plants, miRNA usually binds within the target RNA coding region with a high complementarity degree, and miRNA mainly promotes the cutting and subsequent degradation of target RNA. In animals, translational inhibition predominates, and miRNA usually binds with a lower complementarity degree at multiple points in the 3' non-translatable region of target RNA [64-66].

The described genes in which their expression is regulated by miRNA are frequently transcription factors and genes involved in development [6]. In A. thaliana plants, serious morphological and developmental alterations appear with gene alterations involved in the synthesis and function of miRNA, which indicates the importance of gene regulation by miRNA. With the discovery of new miRNAs, it may be concluded that these molecules may be involved in other cellular processes besides developmental regulation, such as mechanisms of cellular homeostasis or even in defense against viruses [67]. In humans, it has been estimated that regulation by miRNA may affect up to one-third of all genes, which shows the great relevance of this type of mechanisms in cellular functioning [68-70]. Gene regulation by miRNA may have several advantages over other gene regulation mechanisms. The downregulation of gene expression through miRNA is much faster than regulation by a decrease in its transcription, which would facilitate rapid changes in metabolism or localized changes in specific tissues. A single miRNA can also indistinctly regulate several genes of the same or different metabolic pathway, provided that these genes contain complementary sequences to the miRNA, which facilitates coordination in the expression changes of such genes. In addition, miRNAs allow easy feedback regulation if their target genes are involved in the synthesis or function of the miRNA. For example, the mRNAs of DCL1 and AGO1, which are genes involved in the synthesis and function of miRNA in plants, are in turn regulated by miRNAs [66,71].

Mechanisms of Regulation in Cardiovascular Diseases:

Epigenetic mechanisms and networks of transcription factors essential for the differentiation of cardiac myocytes have

been discovered, however, the epigenome remodeling of these differentiated terminal cells during fetal development, postnatal maturation and disease is unknown. Glisbach, et al. [72], investigated the epigenome dynamics of cardiac myocytes during development and in chronic heart failure, finding that prenatal development and postnatal maturation are characterized by an active CpG methylation cooperation and histone markings in generic and cis-regulatory regions for shape the transcriptome of cardiac myocytes. Additionally, it should be mentioned that pathological gene expression in end-stage heart failure is accompanied by changes in active histone tags without significant alterations in CpG methylation and repressive chromatin tags. Notably, the cis regulatory regions in cardiac myocytes are significantly enriched by variants associated with cardiovascular diseases [72].

The regulatory networks that govern gene expression in cardiomyocytes is being intensively investigated, mainly because the deregulation of the genetic program has a fundamental role in the development of a defective myocardium. Epigenetic modifications and functional RNAs that do not encode proteins (ncRNA) are important contributors to this process. On the other hand, the epigenetic modifications that regulate transcription include posttranslational changes to the histones, the proteins around which the DNA is coiled, as well as modifications in the cytosine residues in the DNA, within the histone changes the acetylation and methylation are the most studied, since they have been reported to be important in cardiac physiology and pathophysiology. Understanding the role of microRNAs has also shown important advances, but the role of long ncRNAs and the connection between ncRNAs and epigenetic modifications in the heart are still poorly defined [73].

Several proteins, other than histones, can be acetylated or deacetylated by HAT and HDAC. For example, a study that sought to measure the extent of lysine acetyl identified 1750 acetylated proteins in MV4-11 cells [74,75], while HDAC, HDAC6 is located almost exclusively in the cytosol [75,76]. Several studies that link the acetylation of lysine with cardiac development or the physiological response (duck) to cardiac stress have shown that the pivotal actions of HAT or HDAC are mediated by their acetylation or deacetylation of histone proteins. For example, mutation of HDACs of class II, HDAC5 and HDAC9 results in embryonic or perinatal lethality with variable penetrance accompanied by defects of the ventricular septum and a thin-walled myocardium, possibly due to superactivation of the transcription factor, enhancer factor of myocytes 2 (MEF2), which are known to interact with Class II HDACs and control the differentiation of cardiomyocytes [77,78]. However, the specific acetylation of histone proteins is also important for cardiac development and function, as is the case of the master cardiac transcription factor, GATA4, which is required for cardiac development [75,79,80] and in the adult heart [81], to boost gene expression by stimulating the acetylation of histone H3 lysine 27 (H3K27ac) [75,82].

Investigations into the enzymes responsible for deposition and removal of histone modifications have shown striking phenotypes in a variety of cardiovascular syndromes. Histone deacetylases (HDAC) are one of the most widely studied families of histone-modifying enzymes in the cardiovascular system. These consist of 4 families, each with different isoforms which, in turn, have different histones and, in some cases, no targets. historical, different cellular locations and different biological functions. Its inhibition has been demonstrated pharmacologically (eg, with trichostatin A or valproic acid) to prevent the proliferation of vascular smooth muscle cells [83,84] (with implications for atherosclerosis [85], attenuate hypertension [86] and improve ischemic injury/reperfusion and post ischemic remodeling [87-90] and to block cardiac hypertrophy in the context of heart failure [91-93]. The molecular dissection of these phenomena, particularly in the context of cardiac growth, has revealed that HDACs are potent hypertrophic modulators: the loss of HDAC9 leads to a prodigious cardiac growth [94]. HDAC4 and 5 regulate the regulation of the calcium/calmodulin dependent protein kinase II gene, [95,96]. HDAC2 regulates the activation of the fetal gene GSK3β (glycogen synthase kinase 3 beta) -Akt-dependent on hypertrophy, [97,98].

Some studies show that DNA methylation plays an important role in hereditary differences in response to the metabolic syndrome [99] and may contribute to cardiac pathology induced by catecholamines [100]. Alterations in DNA methylation and hydroxymethylation have been found in animals [72,73] and humans [101,102] heart failure, associated with changes in the expression of pathological genes. The study of mouse cardiomyocytes suggests that DNA methylation largely obeys the structural characteristics of A / B compartmentalization (defined from gene density, histone tags and other characteristics of open chromatin), where the dynamics of DNA methylation the lineage commitment is enriched in compartments A (active) and the genetic alteration of DNA methylation (through DNMT3a and 3b knockout) does not alter compartmentalization [103], a finding supported by the passive relationship between DNA methylation and chromatin structure, at least in the formation phase [98].

On the other hand, studies on long noncoding RNAs (lncRNAs) in the heart reveal their participation in the growth and maturation of development. For example, Fendrr binds PRC2 and the complex Trithorax/MLL group in the mesoderm, and its exhaustion leads to problems in cardiac and chest wall development [98,104]. For its part, Braveheart, another lncRNA associated with mesoderm, binds to the Suz12 subunit of PRC2 and is required to adequately differentiate the embryonic stem cells in cardiac precursors [98,105] and the lncRNA Upper-hand that regulates the Hand 2 locus in cis facilitates the modifications of chromatin (maintenance of the super enhancer) and the elongation of RNA pol II [98,106]. It has been discovered that other lncRNA play a role in the disease regulation of associated genes. Chaer binds to the Ezh2 subunit of PRC2, and its genetic manipulation leads to the alteration of H3K27me3 levels around pathological genes and cardiac hypertrophy in the mouse [98,107]. An antisense transcript was found at the β-MHC locus (heavy chain of beta-myosin) was associated with that locus in a manner independent of the PRC subunit EZH2 in the context of pressure overload [98,108]. Interestingly, that same document showed that the EZH2 interaction with chromatin was regulated by the non-coding RNA

pri -miR-208b, implying a broader role for non-coding RNAs in the regulation of chromatin [98,109].

In conclusion, the mechanisms of gene regulation constitute a well-defined complex and a well-structured machinery that guarantees the maintenance of cell integrity by efficiently controlling several levels of pathological processes and by improving survival. At heart, although many of the regulatory mechanisms are still unknown, these are very important for the differentiation, maintenance and survival of cardiac cells.

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Conflicts of Interest

The author declares no conflict of interest.

References

1. Reece JB, Urry LA, Cain ML, Wasserman SA, Minorsky PV, et al. (2011) Stages in gene expression that can be regulated in eukaryotic cells. In Campbell Biology 10th ed: 365.
2. Overview: Eukaryotic gene regulation, 2018.
3. Acosta-Viana KY, Zavala-Castro JE (1996) Proteínas de unión a DNA. Rev Biomedica 7: 163-172.
4. Bartel DP, Chen CZ (2004) Micromanagers of gene expression: the potentially widespread influence of meazoan microRNAs. Nature Reviews Genetics 5: 396-400.
5. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116: 281-297.
6. Weaver RF (2011) Molecular Biology. 5th Ed.
7. Neissa JI, Guerrero C (2004) Del código genético al código epigenético: Nuevas estrategias terapéuticas. RevFac Med Univ Nac Colomb 52: 287-303.
8. Zhang Y, Fang H, Jiao J, Xu W (2008) The Structure and Function of Histone Deacetylases: The Target for Anti-Cancer Therapy. Curr Med Chem 15:2840-2849.
9. Baulcombe D (2004) RNA silencing in plants. Nature 431: 356-363.
10. Berger SL (2002) Histone modifications in transcriptional regulation. Curr. Opin. Genet.Dev 12: 142-148.
11. Blaustein M, Pelisch F, Srebrow A (2007) Signals, pathways and splicing regulation. Int J Biochem Cell Biol 39: 2031-2048.
12. Nair J, Godschalk RW, Nair U, Owen RW, Hull WE, et al. (2012) Identification of 3, N (4)-etheno-5-methyl-2'-deoxycytidine in human DNA: a new modified nucleoside which may perturb genome methylation. Chem Res Toxicol 25: 162-169.
13. Wright EP, Lamparska K, Smith SS, Waller ZAE (2017) Substitution of Cytosine with Guanylurea Decreases the Stability of i-Motif DNA. Biochemistry 56: 4879-4883.
14. Fischer U, Backes C, Raslan A, Keller A, Meier C, et al. (2015) Gene amplification during differentiation of mammalian neural stem cells in vitro and in vivo. Oncotarget 6: 7023-7039.
15. Bobrowicz AJ, Lightowlers RN, Chrzanowska-Lightowlers Z (2008) Polyadenylation and degradation of mRNA in mammalian mitochondria: a missing link? Biochem Soc Trans 36: 517-519.
16. Ma J (2011) Transcriptional activators and activation mechanisms. Protein Cell 2: 879-888.
17. Jenster G (1998) Coactivators and corepressors as mediators of nuclear receptor function: an update. Mol Cell Endocrinol 143: 1-7.
18. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, et al. (2002) Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci 99: 15524-15529.
19. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, et al. (2004) Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci USA 101: 2999-3004.
20. Celniker SE, Drewell RA (2007) Chromatin looping mediates boundary element promoter interactions. Bioessays 29: 7-10.
21. Conaway RC, Brower CS, Conaway JW (2002) Emerging roles of ubiquitin in transcription regulation. Science 296: 1254-1258.
22. Crossley M, Merika M, and Orkin S (1995) Self-association of the erythroid transcription factor GATA-1 mediated by its zinc finger domains. Mol Cel Biol 15: 2448-2456.
23. Dalmay T (2008) Identification of genes targeted by microRNAs. Biochem Soc Trans 36: 1194-1196.
24. Duncan DD, Stupakoff A, Hedrick SM, Marcu KB, Siu G (1995) A Myc-associated zinc finger protein binding site is one of four important functional regions in the CD4 promoter. Mol Cel Biol 15: 3179-3186.
25. Egido J, Hernández-Presa MA, Tuñón J, Blancocolio LM, Ortego M, et al. (2000) El factor de transcripción kB (NF-kB) y las enfermedades cardiovasculares. Cardiovascular Risk Factors 9: 92-103.
26. Esteller M (2006) The necessity of a human epigenome project. Carcinogenesis 27: 1121–1125.
27. Fagard M, Boutet S, Morel J-B, Bellini C, Vaucheret H (2000) AGO1, QDE-2, and RDE-1 are related proteins required for post-transcriptional gene silencing in plants, quelling in fungi, and RNA interference in animals. Proc Natl Acad 97: 11650–11654.
28. Fisher DE, Parent LA, Sharp PA (1992) Myc/Max and other helix-loop-helix/leucine zipper proteins bend DNA toward the minor groove. Proc Natl Acad Sci USA 89: 11779-11783.
29. García CC (2006) Las versátiles proteínas *zinc fingers.* Revista Química Viva 1: 8-18.
30. Giacinti L, Vici P, Lopez M (2008) Epigenome: A new target in cancer therapy. Clin Ter 59: 347-360.
31. Hammond S, Caudy A, G Hannon (2001) Post Transcriptional Gene Silencing by Double Stranded RNA. Nature 2: 110-119.
32. Hannon G. (2002) RNA Interference. Nature 418: 244-251.
33. Hutvágner G, Zamore PD (2002) A microRNA in a multiple-turnover RNAi enzyme complex. Science 297: 2056-2060.

34. Ihor R. Lemischka IR, Pritsker M (2006) Alternative Splicing Increases Complexity of Stem Cell Transcriptome. Cell Cycle 5: 347-351.

35. Konstantinova IM, Tsimokha AS, Mittenberg AG (2008) Role of proteasomes in cellular regulation. Int Rev Cell Mol Biol 267: 59-124.

36. Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, et al. (2002) Identification of tissue specific microRNAs from mouse. Curr Biol 12: 735-739.

37. Lee Y, Ahn C, Han J, Choi H, Kim J, et al. (2003) The nuclear RNase III Drosha initiates microRNA processing. Nature 425: 415-419.

38. Lewis BP, Burge CB, Bartel DP (2005) Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 120: 15-20.

39. Llave C (2004) MicroRNAs: more than a role in plant development? Molecular Plant Pathology 5: 361-366.

40. Lodish H, Berk A, Matsudaira P, Kaiser, Krieger, et al. (2003) Molecular Cell Biology. 5ta edición.

41. Loizou JI, Murr R, Finkbeiner MG, Sawan C, Qi Wang Z, et al. (2006) Epigenetic Information in Chromatin. The Code of Entry for DNA Repair. Cell Cycle 5: 696-701.

42. Murray RK, Bender DA, Botham KM, Kenelly PJ, Rodwell VW, et al. (2013) Bioquímica de Harper. 29˚ Edición.

43. Mühlemann O, Eberle AB, Stalder L, Zamudio Orozco R (2008) Recognition and elimination of nonsense mRNA. Biochim Biophys Acta 1779: 538-549.

44. Dinman JD (2012) Mechanisms and implications of programmed translational frameshifting.WIREsRNA.

45. Korkmaz G, Holm M, Wiens T, Sanyal S (2014) Comprehensive Analysis of Stop Codon Usage in Bacteria and Its Correlation with Release Factor Abundance. The Journal of Biological Chemistry 289: 30334-30342.

46. Nosek J, Tomaska L, Burger G, Lang BF (2015) Programmed translational bypassing elements in mitochondria: structure, mobility, and evolutionary origin. Trends Genet 31: 187-194.

47. Lavoie G, St-Pierre Y (2011) Phosphorylation of human DNMT1: implication of cyclin-dependent kinases. Biochem Biophys Res Commun 409: 187-192.

48. Nair SK, Burley SK (2006) Estructural aspects of interactions within the Myc/Max/Mad network. Curr Top Microbiol Immunol 302: 123-143.

49. Saraswathy N, Ramalingam P (2011) Concepts and Techniques in Genomics and Proteomics.

50. Nathan D, Sterner DE, Berger SL (2003) Histone modifications: Now summoing sumoylation. Proc Natl Acad Sci 100: 13118-13120.

51. Voss AK, Thomas T (2018) Histone Lysine and Genomic Targets of Histone Acetyltransferases in Mammals. Bioessays 40: e1800078.

52. Nerlov C (2007) The C/EBP family of transcription factors: a paradigm for interaction between gene expression and proliferation control. Trends Cell Biol 17: 318-324.

53. Yang R, Liu CF (2015) Chemical methods for protein ubiquitination. Top Curr Chem 362: 89-106.

54. Osley MA (2004) H2B ubiquitylation: the end is in sight. Biochim Biophys Acta 1677: 74-78.

55. Pabo CO, Sauer RT (1992) Transcription factors: Structural Families and Principles of DNA Recognition. Annu Rev Biochem 61: 1053-1095.

56. Panne D (2008) The enhanceosome. Curr Opin Struct Biol 18: 236-242.

57. Palsuledesai CC, Distefano MD (2015) Protein prenylation: enzymes, therapeutics, and biotechnology applications. ACS Chem Biol 10: 51-62.

58. Daniels CM, Ong SE, Leung AK (2015) The Promise of Proteomics for the Study of ADP-Ribosylation. Mol Cell 58: 911-924.

59. Liu C, Yu X (2015) ADP-ribosyltransferases and poly ADP-ribosylation. Curr Protein Pept Sci 16: 491-501.

60. Bütepage M, Eckei L, Verheugd P, Lüscher B (2015) Intracellular Mono-ADP-Ribosylation in Signaling and Disease. Cells 4: 569-595.

61. Poveda AM (2005) El complejo histona acetiltransferasa B de la levadura *Saccharomyces cerevisiae*. Tesis Doctoral. Departamento de Bioquímica y Biología Molecular. Universidad de Valencia, España.

62. Schütze K, Harter K, Chaban C (2008) Post-translational regulation of plant bZIP factors. Trends Plant Sci 13: 247-55.

63. Shiio Y, Eisenman RN (2003) Histone sumoylation is associated with transcriptional repression. Proc Natl Acad Sci 100: 13225-13230.

64. Smardon A, Spoerke J, Stacey S, Klein M, Mackin N, et al. (2000) EGO-1 is related to RNA-directed RNA polymerase and functions in germ-line development and RNA interference in C. elegans. Curr Biol 10: 169-178.

65. Stamm S (2008) Regulation of alternative splicing by reversible protein phosphorylation. J Biol Chem 283: 1223-1227.

66. Verger A, Perdomo J, Crossley M (2003) Modification with SUMO. A role in transcriptional regulation. EMBO Rep 4**:** 137-142.

67. Xie W, Ted Brown W, Denman RB (2008) Translational regulation by non-protein-coding RNAs: different targets, common themes. Biochem Biophys Res Commun 373: 462-466.

68. Zamore PD, Haley B (2005) Ribo-genome: the big world of small RNAs. Science 309:1519-1524.

69. Hammond SM (2015) An overview of microRNAs. Adv Drug Deliv Rev 87: 13-14.

70. Zilberman D (2008) The evolving functions of DNA methylation. Curr Opin Plant Biol 11: 554-559.

71. Oliver C, Pradillo M, Jover-Gil S, Cuñado N, Ponce MR, et al. (2017) Loss of function of Arabidopsis microRNA-machinery genes impairs fertility, and has effects on homologous recombination and meiotic chromatin dynamics. Sci Rep 7: 9280.

72. Gilsbach R, Schwaderer M, Preissl S, Grüning BA, Kranzhöfer D, et al. (2018) Distinct epigenetic programs regulate cardiac myocyte development and disease in the human heart in vivo. Nat Commun 9:391.

73. Greco CM, Condorelli G (2015) Epigenetic modifications and noncoding RNAs in cardiac hypertrophy and failure. Nat Rev Cardiol 12: 488-497.

74. Choudhary C, Kumar C, Gnad F, Nielsen ML, Rehman M, et al. (2009) Lysine acetylation targets protein complexes and co-regulates major cellular functions. Science 325: 834-840.

75. Yerra VG, Advani A (2018) Histones and heart failure in diabetes. Cell Mol Life Sci.

76. Batchu SN, Brijmohan AS, Advani A (2016) The therapeutic hope for HDAC6 inhibitors in malignancy and chronic disease. Clin Sci (Lond) 130: 987-1003.

77. Chang S, McKinsey TA, Zhang CL, Richardson JA, Hill JA, et al. (2004) Histone deacetylases 5 and 9 govern responsiveness of the heart to a subset of stress signals and play redundant roles in heart development. Mol Cell Biol 24: 8467-8476.

78. McKinsey TA, Zhang CL, Olson EN (2002) MEF2: a calcium-dependent regulator of cell division, differentiation and death. Trends Biochem Sci 27: 40-47.

79. Kuo CT, Morrisey EE, Anandappa R, Sigrist K, Lu MM, et al. (1997) GATA4 transcription factor is required for ventral morphogenesis and heart tube formation. Genes Dev 11: 1048-1060.

80. Molkentin JD, Lin Q, Duncan SA, Olson EN (1997) Requirement of the transcription factor GATA4 for heart tube formation and ventral morphogenesis. Genes Dev 11:1061-1072.

81. Bisping E, Ikeda S, Kong SW, Tarnavsaki O, Bodyak N, et al. (2006) Gata4 is required for maintenance of postnatal cardiac function and protection from pressure overload-induced heart failure. Proc Natl Acad Sci USA 103: 14471-14476.

82. He A, Gu F, Hu Y, Ma Q, Ye LY, et al. (2014) Dynamic GATA4 enhancers shape the chromatin landscape central to heart development and disease. Nat Commun 5: 4907.

83. Okamoto H, Fujioka Y, Takahashi A, Takahashi T, Taniguchi T, et al. (2006) Trichostatin A, an inhibitor of histone deacetylase, inhibits smooth muscle cell proliferation via induction of p21(WAF1). J Atheroscler Thromb 13: 183-191.

84. Kong X, Fang M, Li P, Fang F, Xu Y (2009) HDAC2 deacetylates class II transactivator and suppresses its activity in macrophages and smooth muscle cells. J Mol Cell Cardiol 46: 292-299.

85. Zheng XX, Zhou T, Wang XA, Tong XH, Ding JW (2015) Histone deacetylases and atherosclerosis. Atherosclerosis 240: 355-366.

86. Cardinale JP, Sriramula S, Pariaut R, Guggilam A, Mariappan N, et al. (2010) HDAC inhibition attenuates inflammatory, hypertrophic, and hypertensive responses in spontaneously hypertensive rats. Hypertension 56: 437-444.

87. Lee TM, Lin MS, Chang NC (2007) Inhibition of histone deacetylase on ventricular remodeling in infarcted rats. Am J Physiol Heart Circ Physiol 293: 968-977.

88. Granger A, Abdullah I, Huebner F, Stout A, Wang T, et al. (2008) Histone deacetylase inhibition reduces myocardial ischemia-reperfusion injury in mice. FASEB J 22: 3549-3560.

89. Zhao TC, Cheng G, Zhang LX, Tseng YT, Padbury JF, et al. (2007) Inhibition of histone deacetylases triggers pharmacologic preconditioning effects against myocardial ischemic injury. Cardiovasc Res 76: 473-481.

90. Aune SE, Herr DJ, Mani SK, Menick DR (2014) Selective inhibition of class I but not class IIb histone deacetylases exerts cardiac protection from ischemia reperfusion. J Mol Cell Cardiol 72: 138-145.

91. Dual roles of histone deacetylases in the control of cardiac growth. Novartis Found Symp 2004, 259: 132-141.

92. Cao DJ, Wang ZV, Battiprolu PK, Jiang N, Morales CR, et al. (2011) Histone deacetylase (HDAC) inhibitors attenuate cardiac hypertrophy by suppressing autophagy. Proc Natl Acad Sci USA 108: 4123-4128.

93. Kook H, Lepore JJ, Gitler AD, Lu MM, Wing-Man Yung W, et al. (2003) Cardiac hypertrophy and histone deacetylase-dependent transcriptional repression mediated by the atypical homeodomain protein Hop. J Clin Invest 112: 863-871.

94. Zhang CL, McKinsey TA, Chang S, Antos CL, Hill JA, et al. (2002) Class II histone deacetylases act as signal-responsive repressors of cardiac hypertrophy. Cell 110: 479-488.

95. Backs J, Backs T, Bezprozvannaya S, McKinsey TA, Olson EN, et al. (2008) Histone deacetylase 5 acquires calcium/calmodulin-dependent kinase II responsiveness by oligomerization with histone deacetylase 4. Mol Cell Biol 28: 3437-3445.

96. Zhang T, Kohlhaas M, Backs J, Mishra S, Phillips W, et al. (2007) CaMKIIdelta isoforms differentially affect calcium handling but similarly regulate HDAC/MEF2 transcriptional responses. J Biol Chem 282: 35078-35087.

97. Trivedi CM, Luo Y, Yin Z, Zhang M, Zhu W, et al. (2007) Hdac2 regulates the cardiac hypertrophic response by modulating Gsk3 beta activity. Nat Med 13: 324-331.

98. Rosa-Garrido M, Chapski DJ, Vondriska TM (2018) Epigenomes in Cardiovascular Disease. Circ Res 122: 1586-1607.

99. Orozco LD, Morselli M, Rubbi L, Guo W, Go J, et al. Epigenome-wide association of liver methylation patterns and complex metabolic traits in mice. Cell Metab 2015, 21: 905-917.

100. Chen H, Orozco LD, Wang J, Rau CD, Rubbi L, et al. (2016) DNA methylation indicates susceptibility to isoproterenol-induced cardiac pathology and is associated with chromatin states. Circ Res 118: 786-797.

101. Movassagh M, Choy MK, Knowles DA, Cordeddu L, Haider S, et al. (2011) Distinct epigenomic features in end-stage failing human hearts. Circulation 124: 2411-2422.

102. Movassagh M, Vujic A, Foo R (2011) Genome-wide DNA methylation in human heart failure. Epigenomics 3: 103-109.

103. Nothjunge S, Nührenberg TG, Grüning BA, Doppler SA, Preissl S, et al. (2017) DNA methylation signatures follow preformed chromatin compartments in cardiac myocytes. Nat Commun 8:1667.

104. Grote P, Wittler L, Hendrix D, Koch F, Währisch S, 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.

105. Klattenhoff CA, Scheuermann JC, Surface LE, Bradley RK, Fields PA, et al. (2013) Braveheart, a long noncoding RNA required for cardiovascular lineage commitment. Cell 152: 570-583.

106. Anderson KM, Anderson DM, McAnally JR, Shelton JM, Bassel-Duby R, et al. (2016) Transcription of the non-coding RNA upperhand controls Hand2 expression and heart development. Nature 539: 433-436.

107. Wang Z, Zhang XJ, Ji YX, Zhang P, Deng KQ, et al. A long non-coding RNA defines an epigenetic checkpoint for cardiac hypertrophy. Nat Med 2016,22:1131-1139.

108. Mathiyalagan P, Okabe J, Chang L, Su Y, Du XJ, et al. (2014) The primary microRNA-208b interacts with Polycomb-group protein, Ezh2, to regulate gene expression in the heart. Nucleic Acids Res 42:790-803.

109. Mathiyalagan P, Keating ST, Du XJ, El-Osta A (2014) Interplay of chromatin modifications and non-coding RNAs in the heart. Epigenetics 9: 101-112.