Chapter

Epigenetics of Circadian Rhythm Disruption in Cardiovascular Diseases

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Abstract

Circadian rhythm influences the regulation of homeostasis and physiological processes, and its disruption could lead to metabolic disorders and cardiovascular diseases (CVD). CVDs are still the dominant cause of death worldwide, which are related to numerous environmental and hereditary risk factors. Environmental and hereditary factors can clarify a small fraction of the CVD risk discrepancy. Epigenomics is a very bright strategy that will complement the knowledge of the genetic basis of CVDs. Epigenetic mechanisms allow cells to reply promptly to environmental changes and include DNA methylation, histone modification, and noncoding RNA alterations. According to research data, the circadian rhythm regulates many epigenetic regulators. The challenge is to understand how epigenetic events happen rhythmically in tissues that are involved in the development of CVDs. Epigenetic events are possibly reversible through their interface with environmental and nutritional factors, allowing innovative preventive and therapeutic strategies in cardiovascular diseases.

Keywords: circadian rhythm, cardiovascular disease, epigenetics, DNA methylation, histone modification, microRNA

1. Introduction

The word epigenetics comes from the Greek word 'epi' that means above; that is, hereditary variations in phenotype that do exclude alterations in the nucleotide sequence in DNA [1]. Epigenetic mechanisms involve DNA methylation, post-translational histone modifications, and noncoding RNAs (ncRNAs) [1]. Many studies focus on the epigenetic mechanisms of various diseases. Epigenetic processes are essential for the healthy growth and development of an organism [1]. Epigenetic mechanisms are implicated in the expression of circadian genes in the suprachiasmatic nucleus (SCN) neurons and peripheral tissues [2]. The accumulation of lifestyle and age-related epigenetic changes could result in the development of metabolic disorders and atherosclerosis [2].

The influence of epigenetic changes on the cardiovascular system is an essential link between genotype to phenotype diversity [3]. Epigenetic changes are potentially reversible and may be affected by environmental factors, nutrition, as well as gene-environment interactions. Identifying and understanding epigenetic factors represent a new insight into our knowledge of the risks of cardiovascular disease (CVD) [1].

1.1 Circadian rhythm

The circadian clock is a preserved system that allows organisms to adapt to frequent daily variations, such as the day and night and food availability [4]. This center clock receives signals from the environment and coordinates the daily activity of peripheral clocks found in almost all tissues [4]. The molecular clock is vital in maintaining metabolic and physiological homeostasis [5]. The circadian clock is linked to cellular metabolism so that dysregulation of the circadian rhythm can contribute to various pathological conditions such as diabetes, obesity, metabolic syndrome, inflammation, sleep disorders, and CVDs [5–8].

Genome-wide studies show that 10–15% of all transcripts have a circadian pattern in different tissues involved in the control of metabolism, such as the cardiovascular function [4, 6, 8, 9]. The onset of ischemic cardiopathy is irregularly distributed during the day [1, 10, 11]. A chronobiological strategy to heart disease may present new possibilities to enhance drug development to improve therapeutic outcomes [1]. Genetic evidence supports the function of circadian rhythm in the adjustment of metabolism.

1.2 Cardiovascular diseases

Cardiovascular diseases are complex and diverse. They include hypertension, coronary artery disease, heart failure, and stroke and are a main worldwide reason for morbidity and death in advanced economies and carry a substantial economic burden [1, 3, 12–15]. CVDs are associated with a variety of hereditary and variable risk factors, but environmental and genetic impacts may explain a smaller fraction of CVD risk variability [1, 12]. Studies showed that there is a wide range between 40 and 80% of the genetic contribution to the onset of cardiovascular disease [16].

The complex pathogenesis of CVD is due to the abundance of genetic and environmental factors, of which epigenetic changes are a significant factor [3]. Several risk factors of CVD, like diet, smoking, stress, circadian rhythm, and pollution, are related to epigenetic modifications [1]. Disorders such as hypertension, diabetes, and obesity are often utilized to recognize and cure people at increased CVDs risk [1]. Epigenetic modifications are associated with the processes involved in the CVD in humans or directly affect the gene expression involved in a major cardiac complication, myocardial infarction (MI). Hypertension is one of the leading causes of CVDs [3], while insulin resistance is one of the most significant precursors of type 2 diabetes and associated cardiometabolic conditions [17].

Changes in the style of living and diet could decrease the risk of CVDs [14]. Epigenetic factors indicate there is interindividual variability from birth. It can be stable over the life span and is considered to be an initiator of early programming for adult-onset diseases [12, 18]. The understanding of epigenetics in the onset of CVDs may provide a new perspective on diseases [14].

1.3 Epigenetics

Epigenetics studies heritable variations in gene expression that exclude any change in the DNA sequence [16, 19]. Epigenetic changes include modifications of the DNA base, post-translational histone modifications, and ncRNA mechanisms that run in the nucleus [16, 20]. The epigenome moves the genome from a transcriptionally active to a transcriptionally inactive state [4, 21]. Epimutation transmissions occur throughout the life of the individual [2]. The rate of epigenetic variation is higher than that of genetic mutations because the formation of new inherited changes allows adjustment to a new environment [14, 16].

The most studied epigenetic change is cytosine methylation. It is also a method for suppressing gene expression [22]. DNA methyltransferase (DNMT) enzymes perform DNA methylation. DNMTs bind the methyl group to the 5-site cytosine [16]. The methyl group most commonly binds to the cytosine at a CpG site. It is the fundamental and ubiquitous epigenetic mechanism [14]. The DNMT enzyme family, consisting of DNMT1, DNMT3a, and DNMT3b, methylates cytosine into 5-methylcytosine [14]. Promoter methylation is usually connected with inhibition of transcription [14]. DNMT1 controls the mitotic inheritance of methylated DNA, while DNMT3a and DNMT3b are mainly in charge of *de novo* methylation [14]. The different epigenetic modification is DNA hydroxymethylation, including 5-hydroxymethylated cytosines [14]. Different nutritional and lifestyle factors can affect the methylation of particular CpG sites in gene promoters and into adulthood [22].

Nucleosomes are composed of histone proteins around which DNA is wound into chromatin [16]. Nucleosomes consist of eight histone proteins: two dimers of H2A/H2B and two dimers of H3/H4. Each histone has an adjustable amino-acid tail [16]. Histones can change at more than 30 amino acid residues within amino-terminal tails [4]. Histone modifications include various processes such as acetylation, methylation, phosphorylation, sumoylation, and ubiquitination. It has a function in the organization of chromatin composition and gene expression by altering the intensity of chromatin condensation [1, 14, 23]. Histones are mostly acetylated on lysine (K) residues. Histone acetyltransferase (HAT) and histone deacetylase (HDAC) regulate histone acetylation [14]. Histone methyltransferase regulates histone methylation, while histone demethylase catalyzes demethylation. Transcription activation is usually associated with acetylation of lysine residues at histones 3 (H3) and 4 (H4). Depending on the location of the target lysines in the histone tail and the number of methyl groups added, methylation can either activate or inhibit gene expression [14, 24]. Histone phosphorylation is a marker of cell division and has a function in DNA repair, chromatin condensation during division, and regulation of gene expression [14, 25]. The addition of ubiquitin to lysine residues in histones is called ubiquitination and is implicated in DNA repair and control of transcription [14]. Sumoylation is a changeable post-translational adjustment using small ubiquitin-like proteins (SUMO) and has a crucial function in various mechanisms, such as transcription, and cell cycle progression [14, 26].

RNA-based epigenetic mechanisms include long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) [14]. NcRNAs are functional RNAs that do not translate into proteins and play an essential part in epigenetic regulation [14, 16]. The lncRNAs are extremely tissue-specific relative to protein-coding genes [16]. The miRNAs are short (20–22 nucleotides), single-stranded, evolutionarily-conserved ncRNAs that modulate the expression at the post-transcriptional level of more than 50% of cellular genes [13, 14, 27].

Changes in the environment, including temperature, light, and nutritional habits, trigger reversible epigenomic modification that can influence numerous physiological processes [28]. Epigenome-wide association studies (EWAS) provide information about associations between epigenomic perturbations and traits associated with human diseases [29]. EWAS try to evaluate the environmental impact on genetic regulation. The epigenetic variations could explain missing parts of heritability of chronic diseases that have not yet been determined by genome-wide association studies [29].

2. Molecular background of circadian rhythm

The primary clock genes show circadian expression in the SCN, and light is one of the key drivers that can reset the rhythm phases. There are several crucial proteins

in SCN. Transcription activators are aryl hydrocarbon receptor nuclear translocator-like (ARNTL or BMAL1) and circadian locomotor output cycle caps (CLOCK). Transcription inhibitors are period (PER) and cryptochrome (CRY) [30, 31]. Within 24 h, the entire process of activation and inhibition of gene expression takes place [32, 33]. The circadian system controls gene expression through various mechanisms as a basis of global gene regulation. The first is via E-boxes (promoter and enhancer regulatory elements) of oscillator proteins such as CLOCK, ARNTL, and NPAS2 (neuronal PAS domain protein 2). The second mechanism is using other oscillator proteins such as RORα (retinoic acid receptor-related orphan receptor) and REV-ERBα (or NR1D1, orphan nuclear receptor) via REV-ERB/ROR response element (RRE), which are present in the promoters of specific clock-controlled genes (CCGs) (**Figure 1**). The third mechanism is the daily chromatin remodeling [2, 19, 34, 35].

The ARNTL-CLOCK heterodimers enhance *CRY* and *PER* expression, as well as the expression of additional CCGs. Phosphorylated CRY-PER heterodimers repress the action of ARNTL-CLOCK heterodimer. As a result, *CRY* and *PER* gene transcription is decreased during the day, while ubiquitin degradation reduces the CRY and PER protein levels. The PER2 has histone deacetylase activity and modified chromatin structure, followed by transcription termination [36–39]. The new cycle begins with the termination of the ARNTL-CLOCK repression during the day. Casein kinase 1 (CK1) regulates the quantity of CRY-PER heterodimers' phosphorylation or degradation. CK1 controls protein activity via its phosphorylation [40]. An additional negative loop is REV-ERBα. It binds to the RRE of the *ARNTL* and *CLOCK* genes and inhibits their transcription. Overnight, REV-ERBα degrades, and RORα elevates the *ARNTL* gene transcription [2, 32, 41]. ARNTL-CLOCK heterodimers increase transcription of the nuclear receptors *RORα* and *REV-ERBα* and form an additional circadian rhythm loop [31, 42].

Nearly 10% of the transcripts show circadian rhythmicity [19]. Rhythmic expression of crucial metabolic genes is impaired due to clock gene mutations and lead to metabolic disorders [28]. Fasting glucose levels decrease, and insulin sensitivity

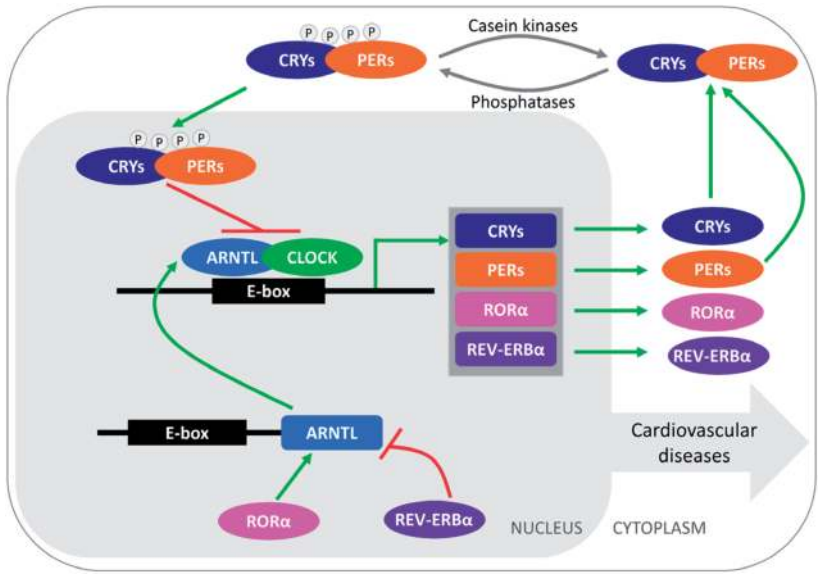

Figure 1.
Circadian rhythm gene regulation in cardiovascular diseases. ARNTL and CLOCK activate transcription of CRY *and* PER *and nuclear receptors (*REV-ERBα *and* RORα*). CRY and PER heterodimerize and phosphorylate by casein kinases and translate into the nucleus where they prevent binding of the ARNTL-CLOCK to the regulatory regions of target genes. In the second feedback loop, REV-ERBα prevents the transcription of* ARNTL*, while overnight the RORα activates transcription of* ARNTL*. ARNTL—aryl hydrocarbon receptor nuclear translocator-like, CLOCK—circadian locomotor output cycle kaput, CRY—cryptochrome, PER—period, P—phosphate, RORα—retinoic-related orphan receptor alpha, Ub—ubiquitin.*

increases in overexpression of the *CRY1* [28]. *ARNTL* deletion and *CLOCK* mutation disturb lipid metabolism [28, 43]. REV-ERBα is involved in liver circadian lipid biosynthesis, and REV-ERBα and ARNTL manage adipocyte differentiation [28]. A primary regulator of bile acid synthesis is REV-ERBα, while the *PER1* and *PER2* deletion upregulates bile acid biosynthesis and causes hepatic cholestasis [28].

Based on circadian rhythms in SCN neurons and peripheral cells, epigenetic mechanisms participate in the formation of circadian rhythms of gene expression [2]. One of the primary circadian genes, CLOCK, has the function of histone acetyltransferase. Chromatin remodeling is an essential underlying mechanism of the clock rhythm and reveals an association between cellular physiology and histone acetylation [2]. ARNTL-CLOCK heterodimer or ARNTL-NPAS2 complex mobilizes HATs and HDACs [28, 44]. To maintain metabolic homeostasis and avoid metabolic disorders, the crosstalk between circadian rhythm and metabolism is necessary [28].

3. Epigenetic changes in circadian rhythm in cardiovascular diseases

Rapid adaptation of cells to environmental changes is facilitated by epigenetic mechanisms that also offer a link between genes and the environment [1]. The phenotypic variations observed in humans are more significant than genotype variations alone, and changes in epigenetic gene modification explain them [1, 45]. CVDs, such as atherosclerosis, cardiac hypertrophy, myocardial infarction, and heart failure, are associated with epigenetic mechanisms ranging from DNA methylation, histone modification, to ncRNAs [13]. An essential way of developing CVD early in life involves epigenetic changes [12]. The underlying mechanism providing the link between the early life environment and the subsequent CVD risk is epigenetic modifications [12].

The association of methylation with specific genes may be useful in assessing the risk of a disease or in monitoring the response to a particular treatment [14]. In the process of DNA methylation, homocysteine, an amino acid that does not enter into protein composition, is essential [46]. The lack of folate in the diet leads to an increase in plasma homocysteine, which contributes to the rise of S-adenosyl homocysteine. It represses transmethylation reactions and decreases methylation all over the epigenome [1, 46]. In atherogenesis are included homocysteine-induced changes in DNA methylation in smooth muscle vascular cells [1, 47, 48]. Endothelial dysfunction and different aspects of CVD are epigenetically associated with folic acid deficiency [16]. Genomic DNA is hypomethylated in human atherosclerotic lesions [1, 2, 12]. Inflammatory processes involved in the development of atherosclerotic plaques are associated with hypermethylation [1, 49]. There are rhythmic changes in global DNA methylation in human blood, and there is an increased level at night [35]. Changes in circadian rhythm genes methylation were observed in aging mice, but are tissue-dependent [35, 50]. For example, in the stomach of older mice, the methylation of the *PER1* promoter decreased, while the methylation of the *ARNTL*, *CRY1*, and *NPAS2* promoters in the spleen was increased [35]. Sleep disorders affect circadian rhythm gene methylation, especially *ARNTL*, *CRY1*, and *PER1* [35, 51]. Temporary epigenetic changes linked with rhythmic gene expression lead to circadian epiphenotypes [2]. Based on this, it can be concluded that DNA methylation may be reversed by conventional drugs, independent of DNA replication [2].

The histone code is involved in many aspects of cardiovascular physiology, from endothelial cell responses to hypoxia to recovery from MI [16]. CLOCK has enzymatic properties of histone acetyltransferase (HAT). It performs acetylation at Lys537 of H3 histone and ARNTL, which is necessary for circadian rhythm [1, 9]. CLOCK works in collaboration with other HATs to maintain circadian rhythm in the acetylation state of histones at CCG promoters [6]. HDAC activity has an essential function in defining

the intensity of myocardial ischemia, especially after MI [16]. Inhibition of HDAC can promote angiogenesis and reduce myocardial damage after MI [16], such as valproic acid (VPA), which is an HDAC inhibitor [2]. Histone deacetylases, SIRT1 (sirtuin 1), and SIRT6 participate in the histone modification, thus controlling gene expression [35] and providing a molecular connection among metabolism and circadian rhythm [6]. SIRT1 deacetylates regulatory proteins and acts as a rhythm-promoting agent in circadian oscillators [35]. SIRT1 has a unique role in central and peripheral circadian rhythms [35]. The purpose of histone phosphorylation in CVDs is minimal [14], while SUMO proteins influence the activity of several essential factors that are important for cardiac development [14]. There are connections between circadian rhythm regulators, chromatin modifications, and cellular metabolism [1, 52].

Numerous lncRNAs have essential regulatory functions in various CVDs [14]. The miRNAs regulate cholesterol metabolism, oxidative stress, and endothelial dysfunction, diverse cellular processes involved in atherosclerosis [14]. MiRNAs may be relevant regulators of circadian rhythm [1]. Circulating miRNA-145 and miRNA-126 are decreased in patients with coronary artery disease, while miRNA-1, miRNA-499, and miRNA-133b are increased during acute myocardial infarction [13]. All those miRNAs can be biomarkers of CVD.

Circadian rhythms combine metabolic and environmental signals and alter gene expression when adapting the organism to particular circumstances [6]. Many epigenetic regulators in some tissues are controlled in a circadian fashion [19, 53]. The challenge is to determine whether epigenetic variations happen in a rhythmic pattern in tissues included in the CVD development [12, 19]. Epigenetics can contribute to enhancing CVD therapies and finding new markers for CVD screening [16, 54].

4. DNA methylation and CVDs

DNA methylation is a durable, relatively constant epigenetic change. It involves the covalent attachment of a methyl group to the cytosine [3, 55]. The primary role of DNA methylation is to regulate gene expression by altering the availability of DNA to the transcription factors [3, 13].

DNA methylation links the steady genome and the changing environment. It is an instrument through which environmental changes influence metabolism [7]. Disruption of DNA methylation has been associated with different metabolic diseases such as diabetes [56], obesity, and insulin resistance [57]. Furthermore, the epigenetic mechanisms control circadian rhythm, and circadian disturbance leads to DNA methylation changes of the clock genes [7, 51, 58]. Adiposity, metabolic syndrome, and weight loss are linked to DNA methylation changes of the *ARNTL*, *CLOCK*, and *PER2* gene promoters [7]. It indicates the significance of determining the impact of DNA methylation in epigenetic studies in complex human disorders [7].

DNA methylation is cell- or tissue-specific, but epimutations are not restricted to the affected tissue and may also be observed in peripheral blood [7]. Compared to other genes, the regulatory regions of circadian rhythm genes are plentiful in CpG sites [59, 60]. Patients with coronary artery disease have altered methylation patterns relative to controls [1, 61, 62]. All mentioned supports the assumption that epigenetic variations are associated with an increased CVD risk [1].

Epigenetic alterations of circadian genes are related to obesity and metabolic disorders [17, 63]. A positive association was found between the alteration of the *ARNTL* gene methylation and weight loss, and its activity is included in the control of adipogenesis and lipid metabolism [63]. The long-term shiftwork, associated with obesity and metabolic syndrome risk, induces hypomethylation of the *CLOCK* gene promoter [22]. *CLOCK* gene SNPs are associated with a

predisposition to metabolic syndrome [22, 64]. Long-term shift work, obesity, and metabolic syndrome are associated with *CRY2* hypermethylation in peripheral blood [22]. Genetic variants of the human *PER2* gene are related to abdominal obesity and CVDs [22, 65]. The methylation status of CpG sites in the *PER2* gene is associated with obesity, metabolic syndrome, and weight loss [7, 22].

Global hypomethylation of DNA is present in atherosclerotic lesions [3, 66]. The severity of atherosclerotic lesions correlates with DNA methylation [3, 14, 67, 68]. There are notable variations in DNA methylation after an MI event [69, 70]. DNA methylation status in blood samples is related to CVD [71, 72].

Environmental and behavioral factors, such as inflammation, smoking, physical activity, or stress, can alter the epigenome [63, 73]. Elevated gene expression in the inflammatory pathway is associated with decreased gene methylation [46]. DNA methylation relies on the accessibility of methyl groups obtained from methionine, and the existence of certain nutrients in the food influences epigenetic changes with possible cardiovascular outcomes [46]. Although methylation changes are related to healthy aging, they could be in the background of the development of some diseases, such as CVD [46, 74]. Reduction in global DNA methylation occurs throughout the human lifespan [46].

5. Histone modification and CVDs

Post-translational modifications occur at amino acid residues in the amino-terminal regions of histone and cover histone acetylation, methylation, phosphorylation, sumoylation, and ubiquitination. It controls chromatin remodeling and gene expression [3, 23]. Histone acetylation is a sign of transcription activation [75], while histone methylation can both stimulate and inhibit transcription [28, 75]. Post-translational histone modifications control genes coding clock proteins [46, 75]. Epigenetic irregularities are related to different disorders, including atherosclerosis [4, 76].

Histone modifications occur at the CCG promoters in a circadian fashion [4, 44, 77, 78]. The core clock protein, CLOCK, has HAT activity. It revealed the molecular association among epigenetic mechanisms and circadian rhythm [4, 19, 59, 79]. CLOCK acetylates ARNTL, which facilitates CRY-dependent repression [19, 28], and interaction of CRY1 with the ARNTL-CLOCK heterodimer [9]. CLOCK and NPAS2 attract different HATs to the promoter of the *PER1* in vascular tissues [59, 78]. The rhythmic binding of ARNTL and CLOCK transcriptional activators directly influences the acetylation of specific histone lysine residues near the DNA-binding site without the involvement of additional HAT enzymes [59]. CLOCK acetylates additional non-histone proteins that have crucial roles in the regulation of different cellular events [4].

SIRT1 is an NAD + -dependent histone deacetylase [4, 59, 80]. It is needed for rhythmic transcription of some clock genes, such as *ARNTL*, *CRY1*, and *PER2* [80, 81]. STIR1 represents the molecular connection between metabolic processes, chromatin remodeling, and circadian physiology [4]. SIRT1 plays a crucial role in metabolism. It deacetylates some proteins of the metabolic pathways and regulates gene expression by histone deacetylation [75]. *SIRT1* expression levels are nearly constant over 24 h, just like relatively constant *CLOCK* gene expression levels*** [4, 82–85]. The HAT function of CLOCK is balanced by SIRT1, which deacetylates H3 and ARNTL, and PER2 [79, 83, 86]. SIRT1 binds to ARNTL-CLOCK within a chromatin complex that, in a circadian fashion, binds to CCG promoters [4, 87]. ARNTL and PER2 are SIRT1 targets [4]. SIRT1 associates with ARNTL-CLOCK heterodimers and improves the deacetylation and degradation of PER2 [86]. SIRT1 deacetylates clock proteins in a circadian fashion [4]. HDAC3 is a deacetylase that modulates histone acetylation of circadian genes, especially those included in lipid

metabolism, such as REV-ERBα [88–92]. Mutations of circadian rhythm proteins that can either modify histones (such as CLOCK) or link to histone modifiers (such as ARNTL, PER2, and REV-ERBα) are related to metabolic syndrome [75, 79]. Endogenous SIRT1 plays a crucial role in mediating cell death/survival processes and is involved in the pathogenesis of the CVDs [28, 93]. The ARNTL sumoylation plays an essential role in ARNTL accumulation and circadian rhythmicity [86].

Histone modifications, and particularly HDACs, have a significant role in the control of vascular homeostasis. Dysregulation of HDAC could lead to the formation of atherosclerotic lesions [14, 94]. In human carotid arteries, histone methylation and acetylation present recognizable patterns depending on the seriousness of the plaque [46]. Inhibition of HDACs leads to reduced inflammation and atherogenesis [46, 95]. In animal studies, HDAC inhibitors reduce the size of MI and ischemia-reperfusion injury after revascularization [46, 96]. The inhibition of HDAC may improve myocardial recovery and block post-infarction remodeling [46]. Fibrosis after MI was reduced by valproic acid, an HDAC inhibitor [14, 97].

6. MicroRNAs and CVDs

MicroRNAs (miRNAs) are small noncoding RNA molecules that repress the expression of target messenger RNAs [1, 3, 5, 98]. MicroRNA dysregulation is associated with cardiovascular diseases, lipid metabolism, endothelial function, ventricular hypertrophy, and post-infarction dysrhythmias [1, 5].

Oscillating microRNAs, based on external triggers, could affect the expression of target genes in a circadian fashion independently of clock genes [5, 99]. In plasma and serum of CVD patients are observed decreased levels of numerous miRNAs, such as miRNA-126, miRNA-17, miRNA-145, miRNA-92a, and miRNA-155 [3].

MiRNAs control the development of atherosclerosis through their action on endothelial function, plaque progression and rupture, and blood vessel development [46]. MiRNA-126 expressed by endothelial cells serves as an adverse adjuster of vascular inflammation, while miRNA-33 plays a vital role in inhibiting the critical genes implicated in cellular cholesterol export [14, 100]. Some miRNAs target DNMTs and thus regulate the level of DNA methylation in atherosclerotic lesions [14]. MiRNA-148 changes HDL and LDL cholesterol levels in murine models and thus has a vital function in lipid metabolism [46, 101, 102].

MiRNA-24, 29a, and 30a influence the circadian rhythm by regulating the stability and translation of PER1 and PER2 mRNAs [5]. The ARNTL-CLOCK heterodimer controls miRNA-142–3p and, in turn, can target ARNTL [5, 103, 104]. MiRNA-21 is a PER2-dependent miRNA and mediates PER2-obtained cardioprotection [5, 105]. Through cellular stress, PER2-dependent miRNA-21 controls cellular glycolysis. Myocardial ischemia causes activation of pathways aimed at increasing the efficiency of myocardial oxygen [5, 106]. Suppression of miRNA-21 reduces the fibrotic response and enhances cardiac activity [5].

A valuable sign of myocardial cell death is the plasma levels of miRNA-208 [3, 107]. MiRNAs have a function in remodeling after MI, a mechanism closely associated with the expansion of tissue fibrosis [14]. A more sensitive biomarker of acute non-STEM MI is miRNA-499 than cardiac troponin T [46].

MicroRNAs could potentially become new modulators of circadian rhythms and could have a positive effect on cardiovascular physiology [5]. MiRNAs regulate about 60% of all human genes [46]. Therapeutic strategies should target specific microRNAs and thus reduce their capacity to inhibit circadian rhythm components or circadian rhythm output genes [5, 108–112]. Administration of microRNAs in a circadian-dependent fashion could serve to adapt the impaired circadian system,

advance metabolism by enhancing efficient oxygen pathways, and thereby promote cardioprotection from ischemia [5].

7. Conclusion

The epigenetic variations of an individual change throughout a lifetime and epigenome profiles, instead of genotypes, are reflected in phenotypes in epigenetic epidemiological studies. Therefore, epigenetic modifications are the reason or a result of a pathological condition. Understanding the epigenetic contribution to CVD pathology may help to develop new treatments and diagnostic approaches. Epigenetic biomarkers might be very useful in treatment monitoring and predicting disease outcome. Epigenetic events can potentially be reversibly altered depending on environmental and nutritional factors. Understanding epigenetic mechanisms may identify valuable, novel biomarkers for disease.

Conflict of interest

The author declares no conflict of interest.

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