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Review

Epigenetic Signalling and RNA Regulation in Cardiovascular Diseases

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Abstract: RNA epigenetics is perhaps the most recent aspect of interest for translational epigeneticists. RNA modifications create such an extensive network of epigenetically driven combination whose role in physiology and pathophysiology is still far from being elucidated. Not surprisingly, some of the players determining changes into RNA structure are in common with those involved in DNA and chromatin structure regulation, while other molecules seem very specific to RNA. It is envisaged, then, that new small molecules, acting selectively on RNA epigenetic changes, will be reported soon, opening new therapeutic interventions based on the correction of the RNA epigenetic landscape. In this review, we shall summarize some aspects of RNA epigenetics limited to those in which the potential clinical translatability to cardiovascular disease is emerging.

Keywords: epigenetics; nucleic acids; RNA; DNA; cardiovascular disease; chronic disease; aging; metabolism

Introduction

Translational epigenetics is a relatively new branch of molecular biology that investigates regulatory processes occurring molecularly "above" the primary DNA sequence associated with physiological and pathophysiological conditions. Specifically, of applied translational epigenetics interest are those mechanisms that introduce functional changes into DNA, RNA, and sometimes proteins, without introducing changes into their primary sequence, and with essential implications in organismal function and disease. Hence, translational epigenetics pays attention to the effect of chemical modifications on DNA [1], histones, non-histone proteins [2], and RNA [3], which in turn result in structural and functional changes of target molecules especially when these molecules may be of therapeutic interest. The object of this review is to explore epigenetic modifications particularly relevant to RNA biology with a particular focus on those crucial in cardiovascular physiology and pathophysiology. For a general description of the regulation and the effects of epigenetic changes occurring at RNA level, the reader is redirected to recent articles that are more detailed in mechanistic terms [4-7].

Among the different RNA species, there are non-coding RNAs (ncRNAs), which are ribonucleic acid sequences that do not codify for proteins. They recently became of interest for their important regulatory function and perspective diagnostic-therapeutic potential. Conventionally, ncRNAs are classified by their length: 200 nucleotides are the cut off between long (lncRNAs) and short non-coding RNAs (sncRNAs). The latter group includes microRNAs (miRNAs) [8]. However, this

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classification is not predictive of ncRNAs function. Indeed, Amaral et al. have proposed a new way to classify ncRNAs based on their biological roles [9]. In fact, many non-coding RNAs, especially lncRNAs, can act as sponges for miRNAs [10], enhancer-associated factors [11], transcriptional repressors [12], and regulators of nuclear structures such as paraspeckles [13]. In this review, for simplicity, we will refer to the classification of ncRNA species according to their length.

Although several reviews have been written about the regulatory role of ncRNAs [14-17] our knowledge is still limited about epigenetic modifications occurring in ncRNAs in physiological and pathological conditions. It is well known, however, that RNA sequences can be the target of methyltransferases such as N6-adenosine_methyltransferase-like 3 (METTL3). In fact, the most common modifications in RNA molecules are the methylation of adenine in position 1 (N^1-methyladenosine, m^1A) [18] and 6 (N^6-methyladenosine, m^6A) [19]. In particular, when m^6A occurs at the 5'-AGG(m6)AC-3' consensus sequence of some mRNAs [20], their stability is modulated [21] and their translation efficiency may be altered [22]. Interestingly, similarly to what occurs to 5-deoxymethylcytosine, the m^6A of RNA can be oxidatively demethylated into N^6-hydroximethyladenosine (hm^6A) and into N^6-formiladenosine (f6A) which may modulate RNA-protein interaction affecting gene regulation [23]. These processes, catalysed at RNA level by the fat mass and obesity associated protein (FTO) in the presence of iron oxide and α-ketoglutarate, are the expression of the deep interplay occurring between DNA, RNA, proteins and cellular metabolism during the process of methylation and demethylation [23] (see **figure 1**). Moreover, ribocytosines can be methylated at position 5 (5-methylcytosine, m5C) [24] by RNA methyltransferases such as the NOP2/Sun domain family (1-7) [25] but also by some DNA methyltransferase such as the DNA methyltransferase type 2 (DNMT2) [26] that originally was considered a DNA-specific methyltransferase. Lately, Ten-eleven-translocation proteins (TETs, which act similarly on DNA and RNA molecules) were found converting RNA 5mC into 5-hydroxymethylcytosine (5hmC) that facilitates the translation of RNA molecules [27]. TET proteins are Fe(II) and α-ketoglutarate-dependent dioxygenases [28] further emphasizing the interconnection between cell metabolism and the epigenetic machinery controlling nucleic acids modifications (see **figure 2**). Of note, methyl groups can be added on riboguanosine too, in particular at position 7′ generating the 7-methylguanosine (m^7G) [29]. This modification mainly occurs on capped [30] and recapped mRNAs and is mediated by canonical mRNA capping methyltransferase (RNMT) which regulates mRNA translation into proteins [31] (see **figure 3**). For more detailed mechanistic insights, the readers will be directed to recent comprehensive reviews.

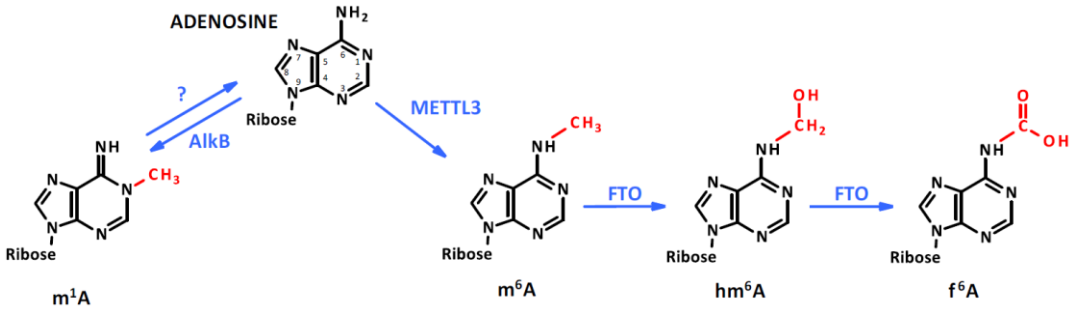

Figure 1. Adenosine methylation. Adenosine can be methylated by the METTL3 in 6th position. In the presence of Fe(II) and α ketoglutarate, the dioxygenase FTO protein oxidates the methyl group generating hm6A and f6A. Meanwhile, the methylation of adenosine in 1st position occurs through an unclear process which can be reverted by AlkB demethylase.

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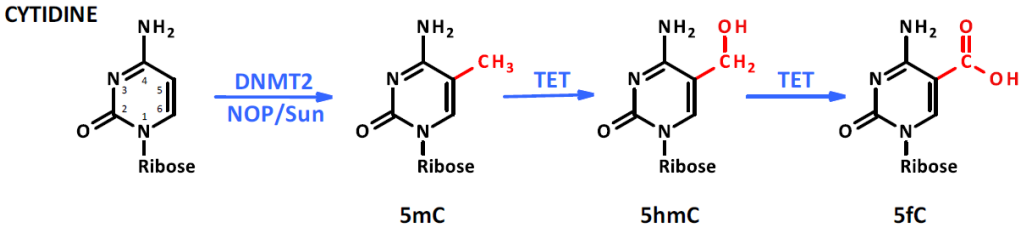

Figure 2. Cytosine methylation. The methylation occurs in 5th position of the molecule by means of DNMT2 or NOP/sun family members. Moreover, in the presence of Fe(II) and α ketoglutarate, TET protein oxidates the methyl group into hydroxymethyl and formyl groups.

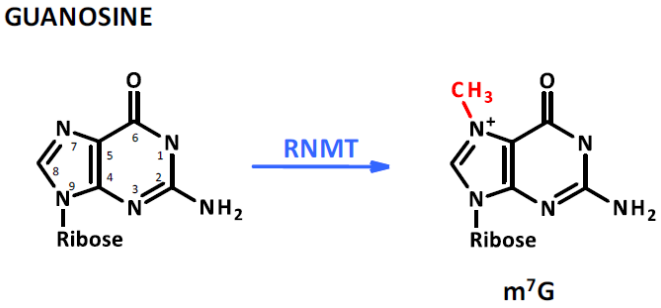

Figure 3. Guanosine methylation. This modification is not as abundant as that of Adenosine and Cytosine, however it is found on capped and re-capped mRNAs by means of RNMT proteins.

mRNAs and ncRNAs methylation in cardiovascular diseases.

Cardiovascular diseases (CVDs) are a pandemic problem that in 2017 caused around 17.7 million deaths worldwide [32]. These disorders are often triggered by chronic metabolic alterations such as those associated with insulin resistance, obesity and diabetes, and are characterized by the presence of small and large vessels disease, heart failure, myocardial infarction and stroke with or without ischemia, hypertension, coronary artery disease, valve disease, arrhythmias, cardiomyopathies (sporadic and congenital), and pericardial diseases [32].

Recently, the American Heart Association identified chronic heart failure as the most important damaging condition for the heart in the aging population [33]. Myocardial infarction and pressure overload are the main causes of heart failure as they may lead to cardiomyocytes hypertrophy and reduced myocardial pump function [34]. In this setting, the m^{6}A RNA methyltransferase METTL3 seems to play a crucial role in eccentric cardiomyocyte remodelling [35]. One of METTL3 target is, in fact, the mRNA encoding for the mitogen-activated protein kinases (MAPKs) resulting in up-regulation of the corresponding protein which in turn induces gene expression, protein synthesis, and increase of cardiomyocyte size [35]. Another work reported about higher level of m^{6}A mRNA in mouse neonatal but not adult cardiac cells. To explore further the role of m^{6}A in this context, METTL3 knockout animals were exposed to pressure overload. Gene-deleted mice were found resistant to the onset of cardiac hypertrophy indicating that the control of RNA methylation is important to prevent the development of heart failure likely by regulating RNA processing [35], (see **figure 4**). Another study showed that the FTO protein decreased in the failing heart resulting, in the presence of hypoxia, in RNA hypermethylation of adenosine increasing the content of m^{6}A [36]. In this study, the downregulation of the FTO protein correlated with alterations in calcium dynamics and, as consequence, the modification of cardiomyocytes contraction, exacerbating in arrhythmic events that are frequently observed in heart failure [36]. The role of m^{6}A in mRNA has been studied in dilated cardiomyopathy and failing heart. This study revealed an increased METTL3 activity and the preponderant presence of RNA transcripts enriched in m^{6}A compared to healthy myocardium. Consequence of this enrichment is higher mRNA instability and reduced expression of genes

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involved in hypertrophic cell growth. This evidence highlighted an unprecedented correlation between the abundance of m^{6}A in RNA and the increase in cellular volume [37]. In failing hearts, one example is given by the m^{6}A hypermethylation of mRNA encoding for Myosin regulatory light chain 2 (Myl2) resulting in lower protein levels than healthy controls [37], suggesting in this case for a destabilizing effect of m^{6}A (see **figure 5**). The destabilizing effect, however, seems context-dependent or, perhaps, associated with specific pathophysiological conditions. Often, in fact, the presence of atherosclerotic plaques correlates with inflammation and macrophages infiltration [38]. A recent work reported about an epigenetic mechanism regulating macrophage function [39]. In this context, METTL3 methylated the signal transducer and activator of transcription 1 (STAT1) mRNA in M1 macrophages [39]. The regions of STAT1 more prone to modification were the coding sequence and the 3'-untranslated region overall increasing the relative mRNA stability [39]. As a result, the methylation of STAT1 mRNA, increasing STAT1 translation and activity, seemed driving M1 macrophage polarization, defining a potentially novel anti-inflammatory signalling pathway [39], (see **figure 4**).

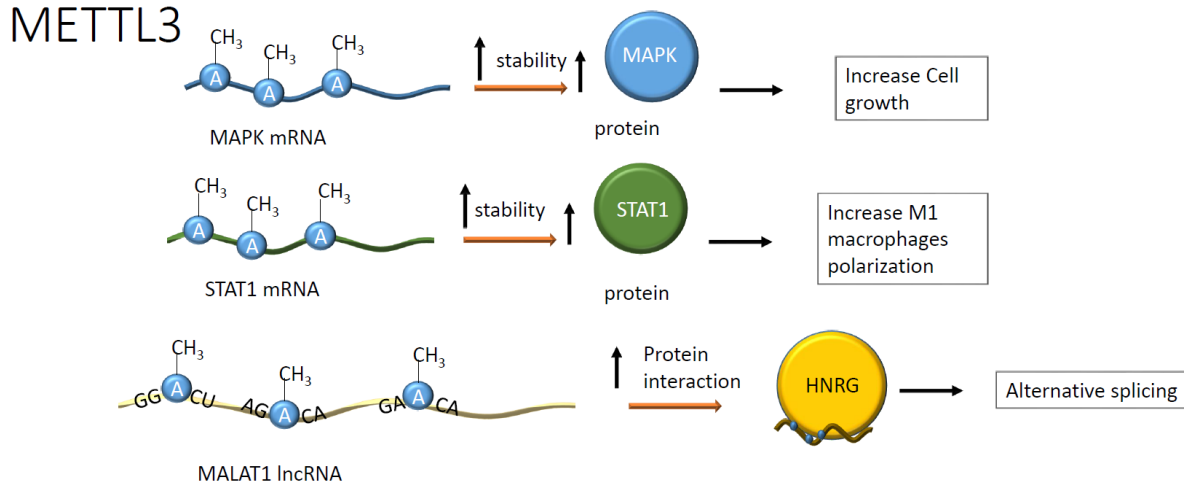

Figure 4. Positive effects on RNA stability and protein interaction upon Adenosine methylation. Positive effects have been reported on MAPK and STAT1 mRNAs whose translation was enhanced. In addition, the methylation in specific ApC sequences on MALAT 1, increases the interaction with HNRG proteins contributing to the alternative splicing.

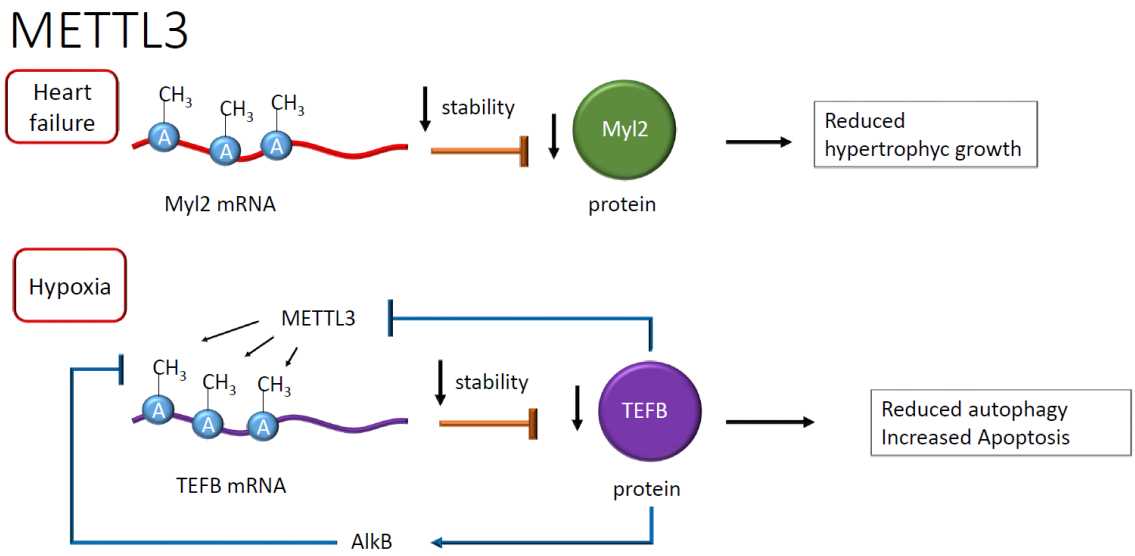

Figure 5. Negative effects on RNA stability after adenosine methylation. Reduced mRNA stability have been reported in hearth failure (HF) and in the presence of hypoxia. In HF, the down regulation

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of Myl2 reduces the hypertrophyc growth, whereas in hypoxia lower levels of TEFB have a negative feed back on its mRNA methylation reflecting the reduction of autophagy and an increase of apoptosis.

Inflammatory signals are at the basis of all chronic diseases and they are often triggered by dysmetabolic conditions associated with aging, a process widely defined as inflammaging [40]. In an experimental model of prolonged hyperglycemia and cardiomyopathy, high levels of the metastasis-associated lung adenocarcinoma transcript-1 lncRNA (MALAT1) have been reported [41]. In this condition, the inhibition of *phosphodiesterase 5, through the administration of sildenafil, resulted in an increase of nitric oxide that normalized MALAT1 levels* in cardiomyocytes *by an unknown mechanism [41]. Interestingly, MALAT1 transcript has multiple sites of adenosine methylation especially on consensus sequences such as GGACU, AGACA, and GAACC [42]. Such modification introduced conformational changes in the RNA molecule promoting its association with multiple RNA binding proteins [43]. As an example, the association with* heterogeneous nuclear ribonucleoprotein G [44] induced pre-mRNA processing and alternative splicing [45]. *Moreover, myeloid cells from MALAT-1 deficient mice displayed a higher adhesiveness to atherosclerotic lesions, and lower levels of MALAT-1 expression in human plaques could be related to worse prognosis caused by the infiltration of inflammatory CD45+ cells [46]. In addition, a role for MALAT1 has been proposed in myocardial infarction (MI) where its expression is up often regulated [47]. In fact, the knockdown of MALAT1, promoted the* progression of cardiomyocytes trough the cell cycle and suppressed apoptosis *via* modulation of the miR-200a-3p/PDCD4 axis [47], (see **figure 4**).

In the context of regulatory processes, it emerged clearly that positive and negative feedback loops are present during the process of RNA maturation in which methylation might play a role at different levels. For example, the expression of miRNAs is frequently regulated by methylation of the corresponding DNA locus. The transcription of miR-200 family members requires, in fact, DNA demethylation at promoter level and is enhanced by reducing the activity of DNMTs [48]. In a rat model of cardiac fibrosis and abdominal aortic constriction [48] miR-200b inhibited the expression of LC3BII/I, which is a trigger signal in cardiac myofibroblast conversion, a process that increases autophagy. Notably, a recent observation suggested a role for m^6A RNA during autophagy in cardiomyocytes [49] subjected to hypoxia and reoxygenation. This is a condition that upregulates METTL3, resulting in methylation of m^6A in the mRNA encoding for the transcription factor EB (TEFB), which is involved in lysosomal biogenesis [49], and repression of protein synthesis [49]. A process eventually leading to reduced autophagy and increased apoptosis [49]. Interestingly, an RNA demethylase named AlkB homolog 5 (ALKBH5) removes the methyl group in TEFB mRNA adenosine. ALKBH5, in physiological conditions, is transcriptionally activated by TEFB itself, which binds ALKBH5 promoter realizing a positive feedback loop controlled at RNA methylation level [49] (see **figure 5**).

In a series of *in vitro* experiments performed by using human umbilical vein endothelial cells in the presence of oxidised low density lipoproteins and platelet-derived growth factor, miR-125b was down regulated whereas podocalyxin (PODXL), a member of the cluster of differentiation 34 of sialomucins, resulted upregulated [50]. Interestingly, miR-125b is repressed in atherosclerosis and, consequently to increased PODXL activity, the vascular endothelium expressed pro-adhesive proteins such as cadherin and ICAM-1 [50]. On the contrary, in vascular smooth muscle cells (VSMC), it has been demonstrated that the upregulation of miR-125b correlates with atherosclerosis, possibly through the activation of transcription factor SP7, which regulates the transdifferentiation of VSMC into osteoblast-like cells. The methylation of pre-miR-125b seems to be an essential mechanism of regulation in this context. Methylation occurring by NOP2/Sun domain family member 2 (Nsun2) represses the formation of mature miR-125b by adding a methyl group on the adenosine present in RRACH and AAC motifs [51]. Notably, in endothelial cells, Nsun2 is known to methylate the transcript encoding the intercellular adhesion molecule 1 (ICAM-1), increasing the corresponding protein's synthesis and enhancing leukocytes adhesion to the endothelial layer [52]. Noteworthy, in vascular smooth muscle cells and endothelium, the down-regulation of Nsun2 protects against the exacerbation of inflammation suggesting a pivotal role for mRNA methylation in the pathogenesis of atherosclerosis [52, 53]. Whether a differential methylation process is active in endothelial or vascular

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smooth muscle cells is at present unknown. However, dysmetabolic conditions or metabolic risk factors are well documented as able to modify the epigenomic landscape [54]. Hence, we may postulate that metabolic alterations associated with atherosclerosis may be implicated in the regulation of ncRNA processing leading to the onset of specific pathophysiological conditions.

Hyperhomocysteinemia (HHcy) is a metabolic alteration often associated with inflammation and frequently detected in cardiovascular and chronic diseases. Of interest, the effect of HHcy seems mediated by Nsun2, which, in T cells, methylates the mRNA encoding for IL-17A [55]. The methylation occurs on m5C present in the mRNA coding region and results in enhanced IL-17A translation suggesting that the modification is pivotal to protein synthesis indirectly contributing the onset of inflammation [55]. Indeed, IL-17A has been correlated with atherosclerotic plaque formation [56]. Consistently, high levels of IL-17A have been found in B and T cells, in macrophages, and plasma cells present within atherosclerotic lesions. Moreover, IL-17A synthesis has been positively associated with plaque vulnerability [56] (**figure 6**).

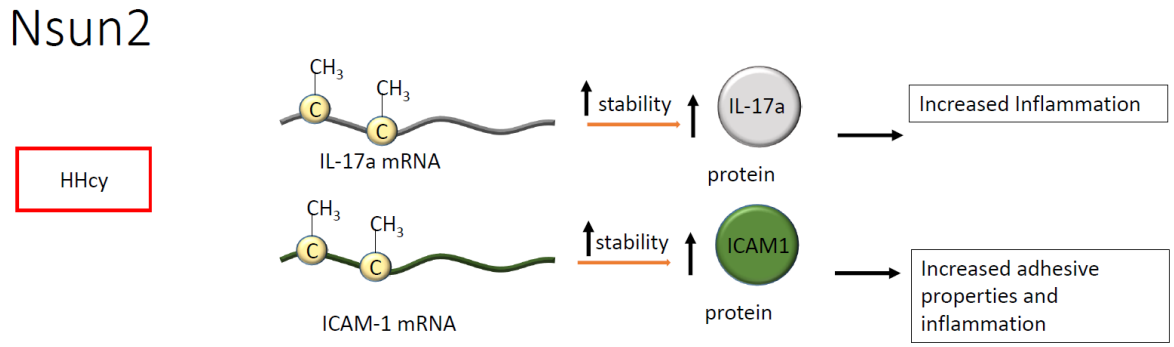

Figure 6. Methylation of Cytosine by Nsun2 in HHcy increases the stability of IL 17a and ICAM1 mRNAs indicating a global increase of inflammation.

Methylation at ncRNA promoters and its consequences for CVDs

HHcy is also a condition where the methylation of lncRNA H19 plays an important regulatory role [57]. In fact, in rodents, the differentially methylated domain located in H19 promoter results hypomethylated in the presence of HHcy, altering the expression of H19 and that of insulin growth factor 2 (IGF2) which is located in proximity [57]. In rats, HHcy determines tissue-specific alterations of methylation at the level of the H19 promoter. In particular, H19 promoter methylation has been observed in rat aorta, while low levels have been found in the liver [57]. The expression of this lncRNA directly inhibits S-adenosylhomocysteine hydrolase (SAHH), which hydrolyzes S-adenosylhomocysteine (SAH) that, in turn, act as an inhibitor of S-adenosylmethionine (SAM)-dependent methyltransferases [58].

Interestingly, when SAH binds DNMT3B, this methylase does not methylate its targets anymore. One of these targets is the NCTC1 coding and promoter region that in turn controls H19 expression determining the so-called promoter competition [58]. As a result, H19 expression level will change interfering with miR-29b [59] and miR-877-3P[60] with consequences for endothelial function [61] and cardiomyocyte apoptosis [59] leading to higher risk of abdominal aortic aneurism [62] and adverse outcome in myocardial ischemia-reperfusion [63].

In summary, the methylation of H19 locus has effects on H19 expression and function and interferes with the activity of DNA methylases determining changes in the expression level of other genes with potential consequences on cardiovascular homeostasis. (see **figure 7**)

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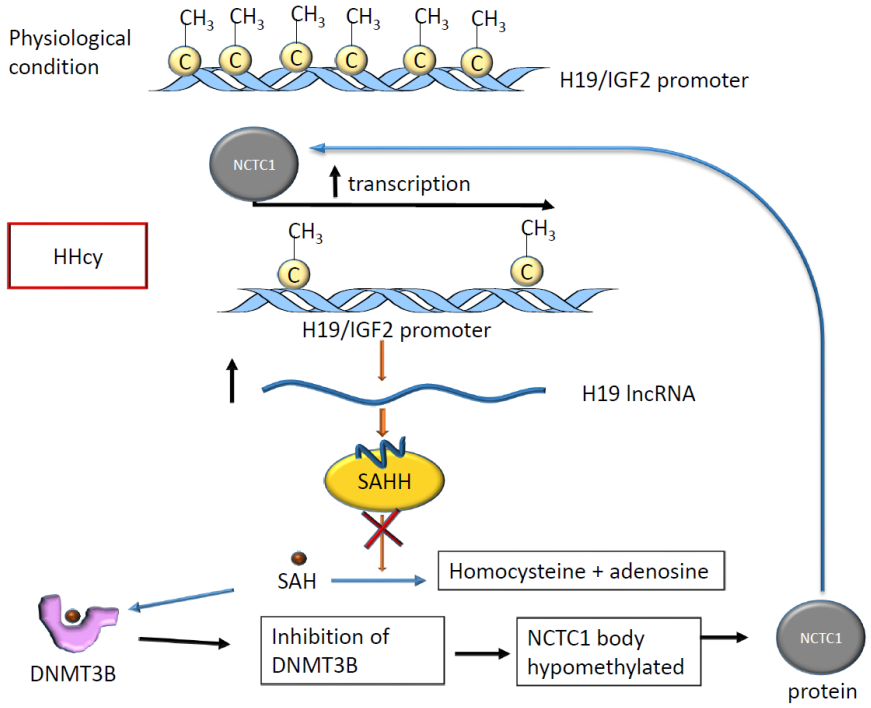

Figure 7. The hypomethylation of H19 promoter in HHcy alters the activity on SAHH enzyme which is inhibited by the binding with H19. The accumulation of SAH inside cells, increases binding between SAH and DNMT3B determining DNMT3B inactivation. As result, the NCTC1 gene is not methylated acting on H19 promoter to determine a positive transcriptional feedback loop.

Other ncRNA species are regulated by methylation at the genomic level with consequences on cardiovascular homeostasis. *In vivo*, miR-145 expression has an impact on atherosclerosis and pulmonary hypertension. High levels of this miR protected blood vessels from plaque formation and hypertension [64, 65]. Hence, the methylation of miR-145 promoter downregulated the expression of the cis-regulated miR preventing its adverse action on the nuclear factor of activated T cells 1 (NFATc1) and CD137 [66]. As a result, VSMCs expressed more nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) that, in turn, activated interleukin 1β (IL-1β) secretion promoting intravascular inflammation [66].

Additionally, miR-145 regulates ubiquitin-like containing PHD and RING finger domains 1 (UHRF1), which interacts with DNA methyltransferase 1 (DNMT1), suggesting an indirect link between miRNA modulation and DNA methylation [67]. DNMT1 was found to methylate miR-145 promoter realizing a negative feedback loop [66] (**figure 8**)

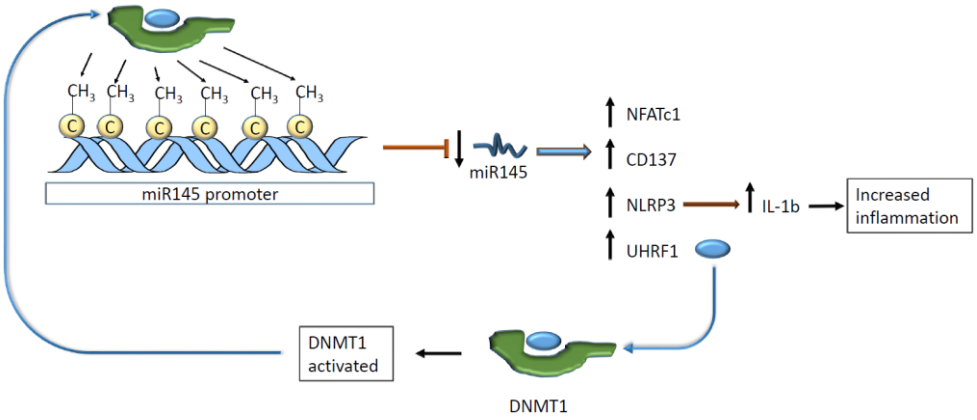

Figure 8. miR145 promoter hypermethylation decreases miR145 levels. This phenomenon results in an up-regulation of different genes enhancing the trascription of cytokines related to inflammation.

Moreover, low levels of miR145 allow the transduction of UTRF1 which is activator of DNMT1 that in turn methylates miR145 promoter activating a negative feedback loop.

Several studies demonstrated the role of methylation in the epigenetic regulation of lncRNAs expression during cardiac development and repair. We provide here a few recent examples of this very recent aspect discussing whether they could be developed as therapeutic targets.

An example is given by the lncRNA named Cardiomyocyte proliferation regulator (CPR) that, if down-regulated, induces cell cycle activation and decreases scar formation after cardiac injury [68]. CPR regulates the **expression of minichromosomal maintenance 3 (MCM3) gene** by recruiting DNMT3A and CpG island methylation on MCM3 promoter [68]. This finding suggests that lncRNA might be the target of a new treatment against myocardial infarction. Another lncRNA, called Antisense non-coding RNA in the INK4 locus (ANRIL), revealed a potential pathophysiological role in overweight newborns (24.6% fat mass at birth) [69]. In this study, umbilical cords were collected at birth, and nine CpG sites were investigated. After nine years, blood pressure, heart rate, and pulse wave velocity of the donors were measured [69]. It was found that ANRIL promoter methylation correlated with heart rate and pulse wave velocity, while blood pressure seemed not linked to ANRIL [69]. This study suggests that non-coding RNAs may be indicator of clinical risk for CVDs development in childhood.

Conclusions

Although the field of epigenetics is rushing forward, most of the epigenetic studies on CVDs and/or chronic diseases are still focused on DNA methylation [70], histone code modifications [71] and the regulation of protein expression and function by a plethora of ncRNAs [72] rather than on the quality, quantity, and role of RNA epigenetic modifications.

Recent literature highlighted the role of mRNA modifications occurring mainly on adenines resulting in increased mRNA instability and repressed protein synthesis [37, 49]. On the other hand, the methylation of mRNA cytosines seems to have a stabilizing effect determining an increase in transduction [55]. It must be said, however, that most of the studies about RNA molecules modified as m^6A and m^5C come from cancer biology leaving cardiovascular diseases relatively unexplored [73-75].

At present, several lncRNAs and miRNAs have been investigated in differential pathophysiological context including hypoxia [47], cardiac regeneration [76], atherosclerosis [64], and in the presence of altered blood pressure [65] but little is known about the consequence of epigenetic modifications on their structure, regulation, and function. The physiological and pathophysiological consequences of RNA modification in adenosine and cytosine and their involvement in CVDs remain mostly unclear [35, 36, 68]. However, this new investigational direction promises to provide insights into unique mechanisms leading to potential new therapeutic discoveries.

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