Novel Insight Into the Epigenetic and Post-transcriptional Control of Cardiac Gene Expression by Thyroid Hormone

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Thyroid hormone (TH) signaling is critically involved in the regulation of cardiovascular physiology. Even mild reductions of myocardial TH levels, as occur in hypothyroidism or low T3 state conditions, are thought to play a role in the progression of cardiac disorders. Due to recent advances in molecular mechanisms underlying TH action, it is now accepted that TH-dependent modulation of gene expression is achieved at multiple transcriptional and post-transcriptional levels and involves the cooperation of many processes. Among them, the epigenetic remodeling of chromatin structure and the interplay with non-coding RNA have emerged as novel TH-dependent pathways that add further degrees of complexity and broaden the network of genes controlled by TH signaling. Increasing experimental and clinical findings indicate that aberrant function of these regulatory mechanisms promotes the evolution of cardiac disorders such as post-ischemic injury, pathological hypertrophy, and heart failure, which may be reversed by the correction of the underlying TH dyshomeostasis. To encourage the clinical implementation of a TH replacement strategy in cardiac disease, here we discuss the crucial effect of epigenetic modifications and control of non-coding RNA in TH-dependent regulation of biological processes relevant for cardiac disease evolution.

Keywords: hypothyroidism, low T3 state, cardiac disease, epigenetic regulators, microRNAs, long non-coding RNAs, T3 replacement, combination therapy

INTRODUCTION

Remodeling of cardiac tissue architecture is the common denominator of a variety of cardiovascular pathologies including myocardial infarction, coronary artery disease, hypertension, cardiomyopathy, and arrhythmias (1). These heart stressors trigger similar adaptive responses leading to hypertrophy of the remaining cardiomyocytes and activation of cardiac fibroblasts and endothelial cells. Although the physiological purpose of these coordinated cellular events is to repair damaged tissue and preserve cardiac performance, persistent activation of the wound healing process is detrimental and facilitates the progression to heart failure (HF). At the molecular level, HF evolution is characterized by a maladaptive down-regulation of the adult cardiac muscle proteins isoforms such as alpha myosin heavy chain (αMHC) and sarcoplasmic reticulum Ca$^{2+}$-ATPase 2a (Serca2a) and a concomitant up-regulation of the fetal genes such as beta myosin heavy chain (βMHC) and phospholamban (Pln) (2).
The adult-to-fetal gene program switch is paralleled by a reduction of the circulating and cardiac levels of 3,5,3′-triiodothyronine (T3), the main biologically active TH. Such a low T3 state condition (LT3S) is considered an independent factor of poor prognosis both in acute and chronic heart disease and is believed to exert a key role in pathological cardiac remodeling and HF evolution (3–5). In line with these observations, maintenance of TH homeostasis in the setting of cardiovascular diseases (CVD), has been proven to be anti-remodeling and promote cardioprotective effects by affecting several aspects of cardiac physiology including contractility, energy production, myocyte geometry, and fate, as well as angiogenesis and matrix remodeling (6–9).

It is now clear that THs exert their effects at multiple levels. Increasing evidence points at TH-sensitive epigenetic and post-transcriptional mechanisms as main triggers of the cellular phenotypes that drives cardiac remodeling (see Figure 1). Epigenetic refers to all changes at the nuclear DNA level, that control DNA structure or conformation without affecting its sequence. The most common epigenetic modifications include post-translational histone modifications, DNA methylation, and non-coding RNA transcripts (10–12). Among these mechanisms, hystone modifications and DNA methylations are able to dynamically alter gene expression by modulating chromatin accessibility to transcription factors and coregulators. In particular, opposite alterations of chromatin structure play a crucial role in the switch of cardiac protein isoforms observed during development, in pathological cardiac hypertrophy and in response to altered TH levels (13–18).

TH-sensitive non-coding RNAs are also involved in silencing and activation of gene expression programs relevant to heart physiology and pathophysiology. It is now appreciated that only around 2% of human transcripts are translated into proteins. Many of the remaining non-protein coding transcripts play a pivotal functional role in cardiac tissue homeostasis, which makes them critical targets of therapeutic strategies. The best characterized non-coding RNA species, microRNAs (miRNAs), are 22–23 nucleotide long molecules that turn off gene expression by blocking the translation or inducing the degradation of target transcripts. miRNAs have been involved in a broad range of pathophysiological processes underlying cardiac contractility, cell fate, response to oxidative stress and myocardial fibrosis (19–24). Long non-coding RNAs (lncRNAs), another emerging class of non-coding RNAs, have a length >200 nucleotides. The abundance of lncRNAs in the cardiovascular system is consistent with their crucial role as part of complex regulatory networks governing heart physiology and pathology (25–27). Of particular interest is the recent concept that a cross-talk between lncRNAs and remodelers of chromatin structure may participate in the regulation of cardiac geometry (28, 29).

Increasing experimental evidence suggests that the above described TH-sensitive epigenetic and post-transcriptional mechanisms are critical triggers of maladaptive cardiac remodeling and HF evolution. To reinforce the importance of maintaining TH homeostasis in the context of cardiac injuries, this review is aimed to comprehensively dissect the contribution of epigenetic modifications and non-coding RNAs to the cardioprotective action of T3.

### CHROMATIN REMODELING IN CARDIOVASCULAR DISEASE: AN OVERVIEW

The function and organization of the genome is dynamically regulated by numerous epigenetic mechanisms that ensure a rapid integration of different signals or inputs (30). Among these mechanisms, post-translational histone modification is crucial to all genome-based activity. Histone proteins are the basic packer and arranger of chromatin structure and can be modified by various post-translational modifications to alter DNA accessibility and gene expression (31). The dynamic transitions between different chromatin conformations rely on a balance between changes that favor a silent state and those that foster a transcriptionally active state (30). In general, histone deacetylation via histone deacetylases (HDACs) allows...
DNA to wrap around histones more tightly, thus inducing a repressive state. On the contrary, histone acetylation via histone acetyl transferases (HATs) induces chromatin relaxation and gene transcription. Abnormal enrichment of these epigenetic marks move the balance between open and closed chromatin conformations, resulting in an altered transcriptional activity that may favor cardiac disease evolution (32).

For example, an increase of HDAC enzymes conveys the cardiac stress signals to the pathological pro-growth gene program observed in in vivo and in vitro models of cardiac hypertrophy and adverse remodeling. Along this line, HDAC inhibitors have proved efficacious in several pre-clinical models of HF (33), leading to a reduction in ischemic/reperfusion (IR) injury and post-ischemic remodeling (34–37), hypertrophy (38–43), fibrosis (44, 45), and inflammation (46, 47). On the other hand, abnormal hystone acetylation via p300 HAT has been involved in salt-induced hypertensive HF (48) and agonist-induced cardiac hypertrophy (49).

Histone methylation, another widespread type of chromatin modification, plays important roles in cardiac lineage specification and differentiation (50, 51), as well as in heart development (52, 53), and pathogenesis of congenital and acquired heart diseases (54, 55). In general, histone 3 methylations at lysine 9 (H3K9) and 27 (H3K27) mark regions of transcriptionally inactive heterochromatin, while histone 3 methylations at lysine 4 (H3K4), 36 (H3K36), and 79 (H3K79) are usually associated with transcriptionally active euchromatin (56). A current model suggests that some methylation marks may dynamically change in response to developmental, environmental or cellular stress cues. Methylated histones are then recognized by chromatin regulators that recruit other factors to alter the promoter accessibility (57). Several histone methyltransferase (HMT) and histone demethylase (HDM) have been identified so far that are differentially expressed during cardiomyocytes differentiation and that are involved in the fetal re-programming of CVD (56).

A further important epigenetic mechanism is the methylation of the DNA cytosine residues at the CpG dinucleotide sequences (58). This epigenetic modification is typically associated with gene silencing, although its effect may be dependent on its location with respect to the target gene. DNA methylation is catalyzed by DNA methyltransferases (DNMTs) (59); of the three DNMTs, DNMT1 is responsible for the maintenance of stable methylation patterns, whereas DNMT3a and DNMT3b catalyze de novo methylation (59).

Comprehensive studies indicate that alterations in DNA methylation profiles contribute to the orchestration of biological processes involved in CVD. For example, in HF patients altered methylation marks have been found in promoter of genes driving myocyte apoptosis, fibrosis and contractility (60). Targeted DNA methylation profiling of cardiac tissue from patients with dilated cardiomyopathy revealed hypomethylation and significantly elevated gene expression of matrix metalloprotease 2 (MMP2) and connective tissue growth factor (CTGF), two genes important for the turnover and stability of the extracellular matrix (ECM) (61). In human ischemic cardiac disease, a genome-wide DNA methylation analysis integrated with RNA sequencing evidenced a transcriptional reprogramming that repressed oxidative metabolism by promoter hypermethylation of genes involved in mitochondrial respiration, kreb cycle, and fatty acid beta oxidation (62). On the contrary, anaerobic glycolytic genes were found to be hypomethylated, altogether depicting a regression to the fetal gene program of substrate utilization (62).

Overall, the above-described findings indicate that a better understanding of the epigenetic mechanisms underlying the regulation of chromatin scaffold may open a new therapeutic avenue to blunt pathological cardiac growth and progression to HF. At this regard, T3 has been found to play a key role in maintaining the adult cardiac gene expression program via recruitment of chromatin remodeling determinants at TH receptors (THR). Therefore, restoring the physiological TH homeostasis under hypothyroidism or LT3S condition may contrast the pathological cardiac gene re-programming.

T3-DEPENDENT REGULATION OF GENE EXPRESSION REQUIRES HYSTONE MODIFICATIONS

THR transcription factors belong to the steroid hormone receptor super-family and are encoded in two genomic loci that produce two different isoforms (THRA and THRB) (63, 64). The THRA1 and B1 isoforms are widely distributed and exhibit overlapping patterns of expression (64). However, the THRA1 is mainly expressed in skeletal and cardiac muscle while the THRBI isoform is more abundant in liver, kidney, brain, and thyroid (63, 64). The use of knock-in animal models harboring THR mutations has provided helpful insight to deciphering the specific role of THRA and B isoforms and distinguishing between canonical and non-canonical cardio-metabolic action of T3. A complete description of this literature is beyond the scope of this review the interested readers are referred to recent papers (65, 66). Briefly, THRA plays a crucial role in post-natal development and cardiac function, whereas THRBI is mainly involved in controlling liver metabolism, the hypophysis pituitary thyroid axis, the circulating levels of TH, and the development of the retina and the inner ear (65). In addition, mice expressing mutant THRIs that cannot bind DNA provided in vivo evidence that relevant physiological effects mediated by THRIs are independent from DNA binding and direct activation of gene expression. These so-called non-canonical TH signaling includes energy metabolism, locomotor activity, and heart rate (66).

When acting through the canonical pathways, THR form homodimers or heterodimers with retinoid X receptor and bind to specific THR response element (TRE) in the regulatory region of the target genes. In contrast to other receptors of the family, unliganded THR localize to nucleus and interact with nucleosome-embedded DNA (67, 68). It has long been recognized that THR are master regulators of the chromosomal structure in driving transcriptional activation or repression (69). THR regulation of gene expression is commonly described by a model of chromatin folding switch (63). On T3-positively regulated target genes, unliganded, chromatin-bound THRIs
interact with transcriptional co-repressors such as Silencing Mediator of Retinoic acid receptor and TH receptor (SMRT) and Nuclear Corepressor-1 (NCoR1) and represses transcription through HDACs recruitment (70–74). Binding of the hormone is supposed to induce a conformational change of THR, leading to detachment of corepressors and binding of coactivators such as Steroid Receptor Coactivator 1 (Src1) or TH Receptor-Associated Protein (TRAP) (75–78). In turn, coactivators recruit p300 HAT and form an open status of chromatin that allows the binding of polymerase II transcriptional machinery and the activation of target gene expression (63, 79–89).

This mechanism of action has important physiological implications in presence of TH dyshomeostasis. At low TH concentrations, as in the presence of hypothyroidism, or low T3 state, the unliganded THR is expected to suppress transcription instead of operating as an inactive, passive receptor. Consistently, hypothyroidism models present a much more severe phenotype than THRA and THR double knockout mouse model (81–84).

The mechanism of transcriptional regulation at negatively regulated THR targets, that are repressed by T3 and activated by unbound THR, is less understood (85). It has been proposed that the corepressors and coactivators act in an opposite manner on this kind of target genes, but the exact underlying molecular mechanism is still unclear (85, 86). Genome-wide profiling of THR binding sites in experimental model of hypo- and hyperthyroidism highlighted additional mechanisms of positive vs. negative regulation of gene expression by T3 (63, 87). These studies demonstrated that: (1) a considerable number of intronic and intergenic regions exists where THR are dynamically recruited upon T3 binding to activate transcription; (2) different DNA binding motifs are preferentially enriched at T3 activated or repressed target sites; (3) T3-facilitated gene repression is associated to reduced chromatin accessibility or decreased THR occupancy (63, 87). In the latter case, transcriptional down-regulation could be mediated by reduced affinity of the T3-liganded THR for specific DNA binding motifs (87).

Notwithstanding being recently revisited and implemented (63, 87), the bimodal switch model of THR-mediated chromatin remodeling still holds true for the antithetical regulation of the myocardial MHC, Serca2a, and phospholamban gene expression observed during cardiac development and disease (15–18, 88–90) (see Figure 1). A role of differential histone acetylation in T3 regulation of myocardial αMHC gene expression was first demonstrated in a hypothyroid rat model (15). In that study, treatment with the HDAC inhibitor trichostatin A (TSA) was unable to switch the MHC expression in the absence of T3. However, TSA potentiated the activation of the αMHC gene when administered along with T3, supporting the hypothesis that an altered histone acetylation is involved in the T3-mediated regulation of MHC gene transcription. Chromatin immunoprecipitation subsequent studies confirmed that TH levels induced specific histone modifications markers at the α and βMHC promoter locus with opposite effect on MHC isoform expression (16–18) (see Figure 1). In particular hypothyroidism determined a reduction of the H3 acetylation and H3K4me marks at αMHC promoter, along with an increase of H3K9met at the same locus. Also, hypothyroidism enhanced βMHC expression by increasing H3 acetylation and H3K4me at the βMHC locus. Reversal of the hypothyroid condition restored the marks of active chromatin on αMHC while repressing them at the βMHC promoter (16–18) (see Figure 1). Interestingly fetal or pathologically-stressed heart showed similar epigenetic marks at the repressed αMHC promoter as observed under hypothyroidism (14). Such outcome requires the activity of the ATP-dependent chromatin remodeler Brahma-Related Gene 1 (Brg1). Brg1 is known to govern two independent pathways that drive cardiac growth and differentiation during development and in pathological condition. In the fetal life a high level of Brg1 maintains myocytes in an embryonic state, with inhibition of αMHC expression and activation of βMHC (12). During cardiomyocyte differentiation Brg1 expression is significantly reduced, facilitating the switch to αMHC expression (12). A re-activation of Brg1 is observed in the adult heart of cardiac patients or experimentally stressed animal models, and drives the hypothyroid-like epigenetic events leading to the pathological α to βMHC switch (14). The opposite effects of T3 and Brg1 in the epigenetic control of MHC isoform expression, along with the different myocardial level of T3 in the fetal and adult heart, suggest an intriguing novel mechanism whereby T3 may affect αMHC myocardial content via antagonizing the Brg1 activity (see Figure 1).

Epigenetic modification is also required for the T3-dependent activation of Serca2a, another important player of myocardial contractility (88) (see Figure 1). Serca2a is a critical determinant of the Ca2+ uptake within the sarcoplasmic reticulum (SR) thus affecting the excitation–contraction coupling. Reduced expression of Serca2a has been widely reported in both systolic and diastolic HF (91–93) while Serca2a overexpression was documented to ameliorate cardiac performance and to reduce the incidence of ventricular tachyarrhythmias (94–96). Therefore, enhanced Serca2a expression is considered a potential master plan to blunt cardiac dysfunction and arrhythmias. However, efficacious pharmacological interventions to restore Serca2a levels are not available, and adenoviral-mediated gene delivery of Serca2a in HF patients failed to rescue the reduced ejection fraction (97). As for αMHC, Serca2a expression at mRNA and protein levels increases after birth in parallel to a surge of T3 level. The decreased expression of Serca2a observed in hypothyroidism can be normalized by restoring the hormonal levels through TH administration (98). In an ex vivo study on human myocardial biopsies, T3 replacement at physiological doses rescued the intracellular flux of Ca2+ that was compromised following long-term T3 deprivation (99). Thus, it is plausible that the LT3S, observed during cardiac disease evolution, may promote Serca2a repression. In line with this interpretation, at Serca2a promoter the liganded THR recruit p300 HAT and TRAP regulators in sequential steps to induce histone acetylation and increase protein synthesis (88).

Serca2a activity is reversibly inhibited by the phosphoprotein Pln, thus modulators of the Serca2a/Pln regulatome are important determinant of Ca2+ cycling kinetics and cardiac contractility (100). It is clearly established that T3 is able to suppress the Pln gene expression in the heart (101–104). There is a tight correspondence between the entity of
Ca^{2+} uptake within the SR and the Pln to Serca2a ratio in hypothyroidism, euthyroidism, and hyperthyroidism conditions, which determines the cardiac performance (103). The precise mechanism of T3 action on Pln remained unclear until the study of Belakavadi and coworkers (90). These authors revealed that T3-dependent down-regulation of Pln in cardiac myocytes is mediated by THR1 and involves the hormone-directed recruitment of HDAC and HDM activities to decrease both histone H3 acetylation and H3K4me1 epigenetic marks (90) (see Figure 1).

T3 AND DNA METHYLATION

In contrast to histone modifications, the effect of TH on DNA methylation is less well-studied. The available data are limited to extra cardiac tissues and suggest the involvement of TH in the regulation of DNA methylating enzymes. Persistent exposure of neonatal rats to antithyroid drug propylthiouracil leads to considerable changes of DNMT expression with increased induction of oxidative stress and up-regulation of p53 in adult liver (105, 106). Newly diagnosed hyperthyroid patients had genome-wide hypomethylation and lower DNMT1 expression in T and B lymphocytes; while relief of hyperthyroidism with antithyroid drugs restored the global DNA methylation and DNMT1 expression (107). These findings raise the intriguing working hypothesis that differential DNA methylation in circulating blood cells could be exploited to stratify patients according to their thyroid state. If validated by dedicated studies, such an approach could be particularly useful to guide better personalized treatment even in patients with milder alteration of thyroid homeostasis such as LT3S.

The role of TH in the direct modulation of DNMT expression has been extensively analyzed in processes that require global changes of tissue architecture such as Xenopus metamorphosis and post-natal neurological development. A recent study showed that the critical gene for de novo DNA methylation, DNMT3a, is controlled by T3 in developing frog tissues. The expression of DNMT3a increased as endogenous plasma T3 rises, and could be induced by exogenous T3 administration (108). The same authors also found that the post-natal surge of T3 levels in mouse brain was paralleled by increased expression of DNMT3a and that the treatment of mouse neuronal cells with T3 caused rapid induction of DNMT3a mRNA (109). Based on these findings it has been proposed that T3 modulation of DNMT3a may represent an evolutionarily conserved mechanism for regulating the post-natal brain differentiation by inducing genome-wide changes in DNA methylation marks. As well as the brain, the heart is a terminally differentiated organ whose post-natal maturation requires a surge of T3 circulating level. Therefore, it can be speculated that similar T3-mediated epigenetic DNA modification as in the brain may be at work to determine heart differentiation. Along this line, it is also conceivable that the LT3S state observed in CVD evolution may favor altered DNA methylation underlying the regression to the fetal gene program. Unfortunately, whether T3-dependent DNA methylation plays a role in cardiac pathophysiology remains an open question that deserves further investigations.

There is, however, emerging evidence indicating that altered DNA methylation may be involved in the setting of myocardial LT3S in patients with CVD. By using RNA-sequencing, it was recently demonstrated that the human myocardium expresses the machinery for TH biosynthesis (110, 111). In patients with ischemic cardiomyopathy, the mRNA levels of thyropheroxidase (TPO), a key component of this TH enzymatic machinery, was reduced in association with reduced T3 levels and altered methylation pattern of the TPO gene (see Figure 1). Also, retrieval of data from methylation analyses in vessel from atherosclerotic patients confirmed similar methylation pattern in the same CpG sites, thus suggesting that altered methylation marks at TPO gene may contribute to the reduced local production of T3 observed in CVD (110).

Finally, an indirect route by which T3 might regulate cardiac DNA methylation, is via interaction with the sympathetic nervous system (SNS). It is well-established that T3 can alter the responsiveness to sympathetic stimulation by enhancing the function and density of the adrenergic receptors within the cardiovascular system. The available data also indicate that activation of adrenergic signaling modulates epigenetic mechanisms of DNA methylation implicated in cardiac hypertrophy and HF (112, 113). These intriguing premises lay the ground for future studies aimed at elucidating the cross-talk between T3 and the SNS in the modulation of cardiac DNA methylation in physiological and pathological conditions.

T3 REGULATION OF CARDIAC MICRONRNAS

Regulation of myocardial miRNA is an emerging mechanism for T3-mediated epigenetic control of cardiac gene expression. As single miRNAs can target several genes within functional related biological processes, controlling the expression of one microRNA can affect whole gene networks and alter the phenotype of complex diseases (20). Accordingly, T3-regulated miRNAs have been shown to counteract many noxious processes underlying adverse cardiac remodeling.

A recent miRNA profiling in hearts of hypothyroid and hyperthyroid mice revealed a signature of T3-responsive miRNAs, including miR-208a, that are predicted to repress the transduction of the prohypertrophic, pathological cascade (114). miRNA-208a is one of the main heart-enriched miRNA that plays a key role in cardiac physiopathology, it belongs to a miRNA family that also comprises miR-208b and its promoter is located in an intronic region of the αMHC gene. Within the heart, miR-208a and miR-208b are implicated in the MHC isoform switch during heart development and disease. In mice hearts physiological levels of miR-208a are necessary for a correct cardiac electrical activity (115). Conversely, cardiac overexpression of miR-208a causes pathological cardiac hypertrophy by targeting TRAP1 and myostatin, that are negative regulators of muscle growth (115). Reduction of myocardial TH levels in cardiac disorders favors αMHC and miR-208a repression while administration of THs to cardiomyocytes in culture significantly upregulates the αMHC/miR-208a expression-ratio and decreases the βMHC/miR-208b expression-ratio (115) (see
remodeling, but also to potentiate protective pathways that preserve mitochondrial quality control and oxidative metabolism including mitochondrial fusion, protein import and folding, mitochondrial antioxidant activity, and carnitine shuttle (122) (see Figure 1). Such data are in agreement with the notion that T3 plays a pivotal role in cellular growth, homeostasis and metabolism (131, 132).

The available evidence on experimental models indicates that the protective cardiac action of T3 is under the synergistic control of T3-responsive miRNAs. Also, a protracted post-ischemic LT3S seems to be a permissive condition for the maintenance of the fetal miRNA program. Such a fetal gene recapitulation contributes to the pathological changes associated with progressive cardiac dysfunction (117, 133). Indeed, in pathological hypertrophy, a striking analogy has been found between the miRNA expression profile found in human HF and that observed in the hearts of 12–14 weeks old fetuses (23). Therefore, based on the published data, a model can be envisioned in which stress stimuli alter the intra-cardiac TH signaling leading to reduced T3 level. In this context, maintenance of T3 cardiac homeostasis through T3 replacement might blunt the dysregulation of T3-dependent miRNAs and their target mRNAs thus limiting adverse remodeling.

T3 REGULATION OF CARDIAC LONG NON-CODING RNA

LncRNAs, another class of non-protein coding DNA products, have been shown to play a major role in many aspects of myocardial gene regulation, especially the epigenetic processes that underpin organogenesis and remodeling of cardiac architecture (134). In particular, lncRNAs have been proposed to bind certain methyltransferases and demethylases and to guide them to specific genomic regulatory regions or to inhibit their interaction with the chromatin scaffold and DNA (134). Among the various species of lncRNA, the natural antisense transcripts (NATs) form an abundant class of regulatory molecules that are transcribed by the opposite strand of protein coding genes. One of them is located within the 4.5-kb intergenic space between the αMHC and βMHC genes and is implicated in the regulation of the MHC switch (135). Within this intergenic region a bifunctional promoter has been found to coordinately control the transcription of the αMHC sense mRNA and βMHC antisense RNA (136). The βMHC NAT extend over the βMHC gene and its promoter. Stimulation of such intergenic transcription has been supposed to silence βMHC sense transcription via RNA-RNA interference to favor the αMHC isoform expression (135, 136). Compelling evidence in hypothyroid and hyperthyroid models indicate that T3 is a positive regulator of this NAT within the myocardial tissue (16, 137). It has been suggested that the T3-dependent NAT binds chromatin repressing complexes such as HDAC and HMT to alter chromatin accessibility at the βMHC promoter (16). According to this model, in pathological condition, reduced T3 levels repress the intergenic NAT along with αMHC gene
transcription while relieving the repression at βMHC gene, which allows a rapid α-to-βMHC switch (16).

Recently a lncRNA, named Myheart (Mhrt), located in the antisense region between the αMHC and βMHC has been found to protect the heart against pathological hypertrophy (28). This action seems not to involve RNA–RNA sequence interference between Mhrt and the βMHC transcript as previously supposed. Instead, Mhrt binds to and represses the activity of Brg1 protein, the chromatin remodeler that triggers the fetal gene reprogramming of cardiac myopathy (28). Following pathologic cardiac stress, the Brg1-HDAC chromatin repressor complex is up-regulated leading to the inhibition of Mhrt transcription and development of cardiomyopathy, which is prevented by reestablishing the pre stress levels of Mhrt (28).

**INDIRECT TRANSCRIPTIONAL REGULATION BY THS VIA SIRTUIN MEDIATED EPIGENETIC MECHANISMS**

Sirtuins (Sirt) are a family of NAD<sup>+</sup>-dependent deacetylating enzymes. Sirt1, the best characterized one, coordinates the metabolic adaptation of the whole organism by modulating the transcription pattern in response to the cell need (138). Several epigenetic mechanisms have been so far identified for Sirt1-mediated regulation of gene expression. Sirt1 can lead to transcriptional repression through direct histone deacetylation, or via methylation of histones and DNA (138). Secondly, Sirt1 can bind and deacetylate a wide range of transcription regulators including TR, thus affecting the expression of target genes positively or negatively (138). Also, Sirt1 deacetylates histone-modifying enzymes to regulate their function. In this manner, Sirt1 interacts with p300 HAT and inhibits its enzymatic activity to promote nucleosomal histones hypoacetylation and alter gene expression outcomes (139).

Sirt1 plays a critical role in CVD physiopathology being involved in the regulation of several cellular metabolic pathways as well as in the death or survival decision making (140). For this reason, Sirt1 is the most extensively studied sirtuin in the cardiovascular system (140). The available literature indicates that Sirt1 can exert beneficial or noxious cardiac effects in a dose dependent manner (140–142). In mouse models of cardiac IR a mild to moderate Sirt1 overexpression (up to about sevenfold) proved cardioprotective by decreasing the pro-apoptotic cascade and increasing the mitochondrial antioxidant defenses (141). On the contrary, excessive Sirt1 up-regulation (more than 10 fold) elicits opposite effects including mitochondrial dysfunctions and low energy production associated to decreased expression of the peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC-1α) (142). These data indicate that to afford cardioprotection the levels of Sirt1 must be rigorously controlled (140).

TH state has been shown to affect Sirt1 activity either directly, by affecting the protein levels, and indirectly, by influencing the cytosolic concentration of NAD<sup>+</sup> that is generated through oxidative phosphorylation (143, 144). Also, Sirt1 is required to promote THR-mediated gene expression. In liver tissue, Sirt1 and THRβ1 interact with each other to enhance T3-responsiveness (145, 146). Accordingly, T3 has been reported to share many metabolic mechanisms with Sirt1 (147, 148) (see Figure 1). Even if the T3-Sirt1 connection has been extensively characterized only in extra cardiac tissue, we recently found that T3 regulates the same antioxidant, anti-fibrotic and pro-survival cardioprotective mechanisms as Sirt1 (122, 142, 149–151), thus suggesting that the T3-Sirt1 cross-talk may be a generalized mechanism to increase the panel of T3-regulated processes under different pathophysiological conditions. Finally, it is worth mentioning the emerging cardio-metabolic action of 3,5 diiodothyronine (T2) via Sirt1 deacetylation pathways (152, 153). T2 is an endogenous active metabolite of T3 that is able to modulate similar processes as T3 in many tissues without manifesting all the deleterious cardiac effect of hyperthyroidism, even when used at pharmacological doses (152, 153). One proposed mechanism of action is the rapid activation of Sirt1 that deacetylates Pgc-1α and Sterol regulatory element-binding proteins-1c (Srebp-1c). These transcription factors then trigger a cascade of events improving mitochondrial biogenesis and energy metabolism, while preventing fat accumulation and diet induced insulin resistance (153). These promising findings encourage further studies to directly explore the therapeutic use of T2 under cardiac disease conditions.

**FUTURE PERSPECTIVES AND CONCLUDING REMARKS**

Overall the available data on T3 cardiac effects should provide helpful guidance to manage hypothyroidism or LT3S conditions optimizing the benefit to risk profile.

Although T3 mediates the vast majority of physiological processes (see Figure 1), LT4 is still considered the unique choice to treat hypothyroidism. Unfortunately, due to altered peripheral conversion of T3 from T4, ~10–20% of patients taking T4 monotherapy experience symptom persistence or recurrence despite normal TH test (154–158). This outcome highlights the need to consider better personalized replacement approaches for a certain patient population. Individualized T3 or combination therapies should be developed to mimic a more physiological intratissutal thyroid hormone signaling. At this regard, the dynamic nature of some epigenetic modifications that are particularly sensitive to altered TH homeostasis, should beexploited by the biomarker discovery research to distinguish patients that may best benefit from T4 monotherapy or combined replacement, thus avoiding the potential adverse effect of thyrotoxicosis.

As a second key point, it has been a long standing dogma that the LT3S in the hyperacute post-IR phase may be beneficial by reducing energy consumption (159). However, increasing clinical and experimental data indicate that the persistence of a LT3S favors cardiac disease evolution and worsens patient prognosis (6, 160, 161). Importantly, to be efficacious against adverse remodeling, the timing of LT3S correction should take into account the regenerative window that is lost in the late post-IR phase (162). Accordingly, T3 administration started 1
week after MI ameliorated heart performance without reversing cardiac remodeling (163). By contrast, THs administered early after IR enhanced cardiac function and prevented left ventricle remodeling (116, 121, 122, 164, 165). These finding are in line with the key role of T3 as main modulator of cardiac repair/regeneration, a process that is critically affected by dynamic epigenetic mechanisms. As for other cardiac epigenetic regulators, such as plant compounds or selected exosomes (166, 167), lower T3 doses proved more efficacious than pharmacological treatments in contrasting the noxious pathways of adverse remodeling (168, 169). Such information on optimized dose and timing for T3 delivery after IR should provide clinically translatable protocol based on inexpensive, commercially available T3.

**AUTHOR CONTRIBUTIONS**

GI and FF conceived the manuscript. FF has written the manuscript with input from all authors. GN and LP contributed analysis of the bibliographic material. All authors have provided critical discussion and have revised the final manuscript.

**REFERENCES**

1. Duygu B, Poels EM, da Costa Martins PA. Genetics and epigenetics of arrhythmia and heart failure. Front Genet. (2013) 4:219. doi: 10.3389/fgene.2013.00219
2. Dirkx E, da Costa Martins PA, De Windt LJ. Regulation of fetal gene expression in heart failure. Biochim Biophys Acta. (2013) 1832:2414–24. doi: 10.1016/j.bbadis.2013.07.023
3. Gerdes AM, Iervasi G. Thyroid replacement therapy and heart failure. Circulation. (2010) 122:385–93. doi: 10.1161/CIRCULATIONAHA.109.917922
4. de Vries EM, Fliers E, Boelen A. The molecular basis of the non-thyroidal illness syndrome. J Endocrinol. (2015) 225:R67–81. doi: 10.1530/JOE-15-0133
5. Janssen R, Müller A, Simonides WS. Cardiac thyroid hormone metabolism and heart failure. Eur Thyroid J. (2017) 6:130–7. doi: 10.1159/000469708
6. Pingitore A, Nicolini G, Kusnic A, Iervasi G, Grigolini P, Forini F. Cardioprotection and thyroid hormones. Heart Fail Rev. (2016) 21:391–9. doi: 10.1007/s10741-016-9545-8
7. Cokkinos DV, Chryssanthopoulos S. Thyroid hormones and cardiac remodeling. Heart Fail Rev. (2016) 21:365–72. doi: 10.1007/s10741-016-9545-7
8. Gerdes AM. Restoration of thyroid hormone balance: a game changer in response to environmental stress: assembly of BRG1-G9a/GLP-DNMT3 regulates heart muscle development and disease. Nat Rev Cardiol. (2017) 14:39–55. doi: 10.1038/nrcardio.2016.174
9. Li B, Carey M, Workman JL. The role of chromatin during transcription. Cell. (2007) 128:707–19. doi: 10.1016/j.cell.2007.01.015
10. Holoch O, Moazed D. RNA-mediated epigenetic regulation of gene expression. Nat Rev Genet. (2015)16:71–84. doi: 10.1038/nrg3863
11. Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. Nat Rev Genet. (2016) 17:487–500. doi: 10.1038/nrg.2016.39
12. Chang CT, Yang J, Han P, Cheng HL, Shang C, Ashley E, et al. Chromatin regulation by Brg1 underlies heart muscle development and disease. Nature. (2010) 466:62–7. doi: 10.1038/nature09130
13. Han P, Li W, Yang J, Shang C, Lin CH, Cheng W, et al. Epigenetic response to environmental stress: assembly of BRG1-G9a/GLP-DNMT3 repressive chromatin complex on Myh6 promoter in pathologically stressed hearts. Biochim Biophys Acta. (2016) 1863(7 Pt B):1772–81. doi: 10.1016/j.bbadis.2016.03.002
14. Han P, DuBun P, Klein I. Effect of serum triiodothyronine on regulation of cardiac gene expression: role of histone acetylation. Am J Physiol Heart Circ Physiol. (2005) 289:H1506–11. doi: 10.1152/ajpheart.00182.2005
15. Haddad E, Jiang W, Bodell PW, Qin AX, Baldwin KM. Cardiac myosin heavy chain gene regulation by thyroid hormones involves altered histone modifications. Am J Physiol Heart Circ Physiol. (2010) 299:H1968–80. doi: 10.1152/ajpheart.00644.2010
16. Pandya K, Pulli B, Bultman S, Smithies O. Reversible epigenetic modifications of the two cardiac myosin heavy chain genes during changes in expression. Gene Expr. (2010) 15:51–9. doi: 10.3727/10522111X129710665735705
17. Pandya K, Kuroki T, Mimura I, Kobayashi M, Wada Y, Kodama T, et al. Distribution of histone3 lysine 4 trimethylation at T3-responsive loci in the heart during reversiblechanges in gene expression. Gene Expr. (2012) 15:183–98. doi: 10.3727/10522111X13375871196989
18. van Rooij E, Sutherland LRB, Qi X, Richardson JA. Control of stress-dependent cardiac growth and gene expression by a microRNA. Science. (2007) 316:575–9. doi: 10.1126/science.1139089
19. van Rooij E, Marshall WS, Olson EN. Toward microRNA-based therapeutics for heart disease: the sense in antisense. Circ Res. (2008) 103:919–28. doi: 10.1161/CIRCRESAHA.108.183426
20. van Rooij E, Sutherland LRB, Th蓟en JJ, Leenders NL, Lentink V, van de Maat M, et al. miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. Circ Res. (2009) 104:170–8. doi: 10.1161/CIRCRESAHA.108.182535
21. Barrington KG, Zamore PD. MicroRNAs: regulating a change of heart. Circulation. (2009) 119:2217–24. doi: 10.1161/CIRCULATIONAHA.107.715839
22. Thum T, Galuppo P, Wolf C, Fiedler J, Knetz S, van Laake LW, et al. MicroRNAs in the human heart: a clue to fetal gene reprogramming in heart failure. Circulation. (2007) 116:258–67. doi: 10.1161/CIRCULATIONAHA.107.887947
23. van Rooij E, Sutherland LRB, Thatcher JE, Di Maio JM, Naseem RH, Marshall WS, et al. Disregulation of microRNAs alter myocardial infarction reveals a role of miR-29 in cardiac fibrosis. Proc Natl Acad Sci USA. (2008) 105:13027–32. doi: 10.1073/pnas.0805038105
24. Barringhaus KG, Zamore PD. MicroRNAs: regulating a change of heart. Circulation. (2016) 134:1484–99. doi: 10.1161/CIRCULATIONAHA.116.023686
25. Poller W, Dimmeler S, Heymans S, Zeller T, Haas J, Karakas M, et al. Non-coding RNAs in cardiovascular diseases: diagnostic and therapeutic perspectives. Eur Heart J. (2017) 39:2704–16. doi: 10.1093/eurheartj/ehx165
26. Uchida S, Dimmeler S. Long noncoding RNAs in cardiovascular diseases. Circ Res. (2015) 116:737–50. doi: 10.1161/CIRCRESAHA.116.302521
27. Han P, Li W, Lin CH, Yang J, Shang C, Nuernberg ST, et al. A long noncoding RNA protects the heart from pathological hypertrophy. Nature. (2014) 514:102–6. doi: 10.1038/nature13596
28. Mathiyalan P, Keating ST, Du XJ, El-Osta A. Interplay of chromatin modifications and non-coding RNAs in the heart. Epigenetics. (2014) 9:101–12. doi: 10.4161/epi.26405
29. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet. (2003) 33(Suppl.):245–54. doi: 10.1038/ng1089
30. Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. Cell Res. (2011) 21:381–95. doi: 10.1038/cr.2011.22
31. Rosa-Garrido M, Chapski DJ, Vondriska TM. Epigenomes in cardiovascular disease. Circ Res. (2018) 122:1586–1600. doi: 10.1161/CIRCRESAHA.118.311597
32. Weeks KL, Avkiran M. Roles and post-translational regulation of cardiac class IIa histone deacetylase isoforms. J Physiol-London. (2015) 593:1785–97. doi: 10.1113/jphysiol.2014.282442
34. Zhao TC, Cheng G, Zhang LX, Tseng YT, Padbury JF. Inhibition of histone deacetylases triggers pharmacologic preconditioning effects against myocardial ischemic injury. Cardiovasc Res. (2007) 76:473–81. doi: 10.1016/j.cardiores.2007.08.010
35. Lee TM, Lin MS, Chang NC. Inhibition of histone deacetylase on ventricular remodeling, in rats. Am J Physiol Heart Circ Physiol. (2007) 293:H968–77. doi: 10.1152/ajpheart.00891.2006
36. Granger A, Abdullah I, Huebner F, Stout A, Wang T, Huebner T, et al. Histone deacetylase inhibition reduces myocardial ischemia-reperfusion injury in mice. FASEB J. (2008) 22:3549–60. doi: 10.1096/fj.08-108348
37. Aune SE, Herr DJ, Mani SK, Menick DR. Selective inhibition of class I but not class II histone deacetylases exerts cardiac protection from ischemia reperfusion. J Mol Cell Cardiol. (2012) 54:138–45. doi: 10.1016/j.yjmcc.2012.04.035
38. Cao DJ, Wang ZV, Battiprolu PK, Jiang N, Morales CR, Kong Y, et al. Inhibition of class I histone deacetylase (HDAC) inhibitors attenuate cardiac hypertrophy by suppressing apoptosis. Proc Natl Acad Sci USA. (2011) 108:4123–8. doi: 10.1073/pnas.1015081108
39. Antos CL, McKinsey TA, Dreitz M, Hollingsworth LM, Zhang CL, Schreiber K, et al. Dose-dependent blockade to cardiomyocyte hypertrophy by histone deacetylase inhibitors. J Biol Chem. (2003) 278:28930–7. doi: 10.1074/jbc.M303113200
40. Gallo P, Latronico MV, Grimaldi S, Borgia F, Todaro M, Jones P, et al. Inhibition of class I histone deacetylase by an apicidin derivative prevents cardiac hypertrophy and failure. Cardiovasc Res. (2008) 80:416–24. doi: 10.1093/ctx/cvn215
41. Kee HJ, Sohn IS, Nam KI, Park JE, Qian YR, Yin Z, et al. Inhibition of class I histone deacetylase blocks cardiac hypertrophy induced by angiotensin II infusion and aortic banding. Circulation. (2006) 113:51–9. doi: 10.1161/CIRCULATIONAHA.105.559724
42. Kong Y, Tannous P, Lu G, Berenji K, Rothermel BA, Olson EN, et al. DOT1L-mediated H3K79me2 modification critically regulates gene in the cardiac lineage. Cell. (2016) 168:4178–83. doi: 10.1016/j.celrep.2016.04.036
43. Ooi JY, Tuano NK, Rafehi H, Gao XM, Ziemen M, Du XJ, et al. HDAC inhibition attenuates cardiac hypertrophy by acetylation and deacetylation of target genes. Epigenetics. (2015) 10:418–30. doi: 10.1080/15592294.2015.1024406
44. Iyer A, Fenning A, Lim J, Le GT, Reid RC, Halili MA, et al. The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. J Biol Chem. (2011) 286:6839–47. doi: 10.1074/jbc.M110.112200
45. Morimoto T, Sunagawa Y, Kasumura T, Takaya T, Wada H, Nagasawa A, et al. The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. J Clin Invest. (2008) 118:868–78. doi: 10.1172/JCI33160
46. Gusterson RJ, Jazrawi E, Adcock IM, Latchman DS. The transcriptional co-activators CREB-binding protein (CBP) and p300 play a critical role in cardiac hypertrophy that is dependent on their histone acetyltransferase activity. J Biol Chem. (2003) 278:6838–47. doi: 10.1074/jbc.M211762200
47. McKinsey TA. Targeting inflammation in heart failure with histone deacetylase inhibitors. Mol Med. (2011) 17:434–41. doi: 10.2119/molmed.2011.00022
48. Shimizu H, Astapova I, Ye F, Bilman M, Cohen RN, Hollenberg AN. NCoR1 and SMRT play unique roles in thyroid hormone action in vivo. Mol Cell Biol. (2015) 35:555–65. doi: 10.1128/MCB.01208-14
49. Wang Z, Li X, Christodoulou D, Seidman CE, Seidman JG, et al. Epigenetic repression of cardiac progenitor gene expression by Ezh2 is required for postnatal cardiac homeostasis. Nat Genet. (2012) 44:343–7. doi: 10.1038/ng.1068
50. FH, et al. Histone deacetylase 3 complex is required for repression by thyroid hormone receptor. Mol Cell Biol. (2003) 23:5122–31. doi: 10.1128/MCB.23.15.5122-5131.2003
51. Tong GX, Jeyakumar M, Taner M, Bagchi MK. Transcriptional silencing by unliganded thyroid hormone receptor beta requires a soluble corepressor.
that interacts with the ligand-binding domain of the receptor. Mol Cell Biol. (1996) 16:1909–20. doi: 10.1128/MCB.16.5.1909

73. Chen JD, Umesono K, Evans RM. SMRT isoforms mediate repression and anti-repression of nuclear receptor heterodimers. Proc Natl Acad Sci USA. (1995) 92:7637–41. doi: 10.1073/pnas.92.19.7637

74. Horlein AJ, Näär AM, Heinzel T, Tonnesen J, Gloss B, Kurokawa R, et al. Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. Nature. (1995) 377:397–404. doi: 10.1038/377397a

75. Lin BC, Hong SH, Krig S, Yoh SM, Privalsky M. A conformational switch in nuclear hormone receptors is involved in coupling hormone binding to co-repressor release. Mol Cell Biol. (1997) 17:6131–8. doi: 10.1128/MCB.17.10.6131

76. Perissi V, Staszewski LM, Invernizzi M, Kurokawa R, Krones A, Rose DW, et al. Molecular determinants of nuclear receptor-corepressor interaction. Genes Dev. (1999) 13:3198–208. doi: 10.1101/gad.13.24.3198

77. Chen H, Lin RJ, Schiltz RL, Chakkaverty D, Nash A, Nagy L, et al. Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. Cell. (1997) 90:569–80. doi: 10.1016/S0092-8674(00)80516-4

78. Fondell JD, Ge H, Roeder RG. Ligand induction of a transcriptionally active thyroid hormone receptor coactivator complex. Proc Natl Acad Sci USA. (1996) 93:8329–33. doi: 10.1073/pnas.93.16.8329

79. Lee KC, Li J, Cole PA, Wong J, Kraus W. Transcriptional activation by thyroid hormone receptor-beta involves chromatin remodeling, histone acetylation, and synergistic stimulation by p300 and steroid receptor coactivators. Mol Endocrinol. (2003) 17:908–22. doi: 10.1210/me.2002-0308

80. Li Q, Imho F, Collingwood TN, Urmov FD, Wolpe AP. P300 stimulates transcription instigated by ligand-bound thyroid hormone receptor at a step subsequent to chromatin disruption. Embo J. (1999) 18:5634–52. doi: 10.1093/emboj/18.20.5634

81. Göthe S, Wang Z, Ng L, Kindblom JM, Barros AC, Ohlsson C, et al. Mouse devoid of all known TH receptors are viable but exhibit disorders of the pituitary-thyroid axis, growth, and bone maturation. Genes Dev. (2001) 15:1227–37. doi: 10.1101/gad.15.12.1227

82. Chattergoon NN. Thyroid hormone signaling and consequences for cardiac development. J Endocrinol. (2019) 242:7145–60. doi: 10.1530/JOE-18-0704

83. Müller OL, Lange M, Rattunde H, Lorenzen H-P, Müller M, Frey N, et al. Transgenic rats hearts overexpressing SERCA2a show improved contractility under baseline conditions and pressure overload. Circ Res. (2003) 93:380–9. doi: 10.1161/01.RES.0000098633.000429-2

84. Greenberg B, Butler J, Pelkonen P, Voors AA, Desai AS, et al. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. Lancet. (2016) 387:1178–86. doi: 10.1016/S0140-6736(16)00882-9

85. Shinoy R, Klein I, Ojaama K. Differential regulation of SR calcium transporters by thyroid hormone in rat atria and ventricles. Am J Physiol. (2001) 280:H1690–6. doi: 10.1152/ajpheart.2001.281.4.H1690

86. Forini F, Polachici A, Pizzorusso T, Ratto GM, Saviozzi M, Vanini V, et al. 3,5,3'-Triiodothyronine deprivation affects phenotype and intracellular [Ca2+]i of human cardiomyocytes in culture. Cardiovasc Res. (2001) 51:322–30. doi: 10.1016/S0008-6836(01)00287-5

87. Kranias EG, Hajri RJ. Modulation of cardiac contractility by the phospholamban/SECA2a regulome. Circ Res. (2012) 110:1646–60. doi: 10.1161/CIRCRESAHA.111.1129754

88. Prunier F, Kawase Y, Pilankatta R. The Ca2+ ATPase pump overexpression in a porcine model of ischemia reperfusion. Circulation. (2008) 118:614–24. doi: 10.1161/CIRCULATIONAHA.108.770883

89. Greenberg B, Butler J, Pelkonen P, Voors AA, Desai AS, et al. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. Lancet. (2016) 387:1178–86. doi: 10.1016/S0140-6736(16)00882-9

90. Kranias EG, Hajri RJ. Modulation of cardiac contractility by the phospholamban/SECA2a regulome. Circ Res. (2012) 110:1646–60. doi: 10.1161/CIRCRESAHA.111.1129754

91. Arya M, Otsu K, MacLennan DH, Alpert NR, Periasamy M. Effect of thyroid hormone on the expression of mRNA encoding sarcoplasmic reticulum proteins. Circ Res. (1991) 69:666–76. doi: 10.1161/01.RES.69.2.666

92. Kirkman Y, Otsu K, Nishida K, Kuzuya T, Tada M. Thyroid hormone enhances Ca2+ pumping activity of the cardiac sarcoplasmic reticulum by increasing Ca2+ ATPase and decreasing phospholamban expression. J Mol Cell Cardiol. (1994) 26:1145–54. doi: 10.1006/jmcc.1994.1133

93. Kranias EG, Hajri RJ. Modulation of cardiac contractility by the phospholamban/SECA2a regulome. Circ Res. (2012) 110:1646–60. doi: 10.1161/CIRCRESAHA.111.1129754

94. Nagai R, Zarin-Herzberg A, Brandl CJ, Fujii T, Tada M, MacLennan DH, et al. Regulation of myocardial Ca2+ -ATPase and phospholamban mRNA expression in response to pressure overload and thyroid hormone. Proc Natl Acad Sci USA. (1989) 86:2966–70. doi: 10.1073/pnas.86.8.2966

95. Bunker SK, Dandapat J, Chainy GBN, Sahoo SK, Nayak PK. Neonatal exposure to 6-α-NPropyl-Thiouracil, an anti-thyroid drug, alters expression of hepatic DNA methyltransferases, methyl CpG-binding proteins, GADD45α, p53, and PCNA in adult male rats. Europ Thyroid J. (2017) 6:281–91. doi: 10.1159/000479681

96. Bunker SK, Dutta A, Pradhan J, Dandapat J, Chainy GBN. Curcumin restores the epatic genomic changes in propylthiouracil (PTU) Induced hypothyroid male rats: a study on DNMTs, MBDs, GADD45α, C/ EBP-βandPCNA. Food Chem Toxicol. (2019) 123:169–80. doi: 10.1016/j.fct.2018.10.050

97. Guo Q, Wu D, Yu H, Bao J, Peng S, Shan Z, et al. Alterations of global DNA methylation and DNA methyltransferase expression in T and B lymphocytes from patients with newly diagnosed autoimmune thyroid diseases after treatment: a follow-up study. Thyroid. (2018) 28:377–85. doi: 10.1089/thy.2017.0301

98. Kyono Y, Sachs LM, Bilesimo P, Wen L, Denver RJ. Developmental and thyroid hormone regulation of the DNA methyltransferase
125. Zhang X, Wang X, Zhu H, Zhu C, Wang Y, Pu WT, et al. Synergistic effects of the GATA-4-mediated miR-144/451 cluster in protection against simulated ischemia/reperfusion-induced cardiac myocyte death. J Mol Cell Cardiol. (2010) 49:841–50. doi:10.1016/j.yjmcc.2010.08.007
126. Wang JX, jiao QJ, Li Q, Long B, Wang K, Liu JP, et al. miR-499 regulates microvascular density by targeting calcineurin and dynamin-related protein-1. Nat Med. (2011) 17:71–8. doi:10.1038/nm.2282
127. Wang Y, Men M, Yang W, Zheng H, Xue S. MiR-31 downregulation protects against cardiac ischemia/reperfusion injury by targeting protein kinase C epsilon (PKCε) directly. Cell Physiol Biochem. (2015) 36:179–90. doi:10.1159/000374062
128. Martinez EC, Lilibana S, Wang P, Vardy LA, Jiang X, Armagam A, et al. MicroRNA-31 promotes adverse cardiac remodeling and dysfunction in ischemic heart disease. J Mol Cell Cardiol. (2017) 112:27–39. doi:10.1016/j.yjmcc.2017.08.013
129. Su M, Chen Z, Wang C, Song L, Zou Y, Zhang L, et al. Cardiac-specific overexpression of miR-222 induces heart failure and inhibits autophagy in mice. Cell Physiol Biochem. (2016) 4:1593–11. doi:10.1007/s00448-015-3650-3
130. Seok HY, Chen J, Kataoka M, Huang ZP, Ding J, Yan J, et al. Loss of MicroRNA-155 protects the heart from pathological cardiac hypertrophy. Circ. Res. (2014) 114:1585–95. doi:10.1161/CIRCRESAHA.114.303784
131. Kress E, Samarut J, Plateroti M. Thyroid hormones and the control of cell proliferation or cell differentiation: paradox or duality? Mol Cell Endocrinol. (2009) 313:36–49. doi:10.1016/j.mce.2009.08.028
132. Lópezm, Alvarez CV, Nogueiras R, Díequez C. Energy balance regulation by thyroid horomones at central level. Trends Mol Med. (2013) 19:418–27. doi:10.1016/j.molmed.2013.04.004
133. Ye Y, Perez-Polo JR, Qian J, Birnbaum Y. The role of microRNA in modulating myocardial ischemia-reperfusion injury. Physiol Genomics. (2011) 43:534–42. doi:10.1152/physiogenomics.00130.2010
134. Schromnock N, Harvey RP, Mättick JS. Long noncoding RNAs in cardiac development and pathophysiology. Circ. Res. (2012) 111:1349–62. doi:10.1161/CIRCRESAHA.112.268953
135. Haddad F, Bodell PW, Qin AX, Giger JM, Baldwin KM. Role of antisense RNA in coordinating cardiac myosin heavy chain gene switching. J Biol Chem. (2003) 278:37132–8. doi:10.1074/jbc.M305911200
136. Haddad F, Qin AX, Bodell PW, Jiang W, Giger JM, Baldwin KM. Intergenic transcription and developmental regulation of cardiac myosin heavy chain genes. Am J Physiol Heart Circ Physiol. (2008) 294:H29–40. doi:10.1152/ajpheart.01125.2007
137. Danzi S, Klein S, Klein I. Differential regulation of the myosin heavy chain genes alpha and beta in rat atria and ventricles: role of antisense RNA. Thyroid. (2008) 7:761–8. doi:10.1089/thy.2008.0043
138. Zhang T, Kraus WL. SIRT1-dependent regulation of chromatin and transcription: linking NAD+ metabolism and signaling to the control of cellular functions. Biochim Biophys Acta. (2010) 1804:1666–75. doi:10.1016/j.bjapap.2009.10.022
139. Bouras T, Fu M, Sauge AA, Wang F, Quong AA, Perkins ND, et al. SIRT1 deacetylation and repression of p300 involves lysine residues 1020/1024 within the cell cycle regulatory domain 1. J Biol Chem. (2005) 280:10264–76. doi:10.1074/jbc.M408748200
140. Bindu S, Pillai VB, Gupta MP. Role of Sirtuins in Regulating Pathophysiology of the Heart. Trends Endocrinol Metab. (2016) 8:563–73. doi:10.1016/j.tem.2016.04.015
141. Hsu CP, Zhai P, Yamamoto T, Masejima Y, Matsuhashi S, Harirahan N, et al. Silent information regulator 1 protects the heart from ischemia/reperfusion. Circulation. (2010) 122:2170–82. doi:10.1161/CIRCULATIONAHA.110.958033
142. Alcendor RR, Gao S, Zhai P, Zablocki D, Holle E, Yu X, et al. Sirt1 regulates aging and resistance to oxidative stress in the heart. Circ. Res. (2007) 100:1512–21. doi:10.1161/01.RES.0000267723.65696.4a
143. Cordeiro A, de Souza LL, Oliveira LS, Faustino LC, Santiago LA, Bloise FF, et al. Thyroid hormone regulation of Sirtuin 1 expression and implications to integrated responses in fasted mice. J Endocrinol. (2013) 216:181–93. doi:10.1530/JEO-12-0420
144. Xu QY, Wang XL, Peng YF. Hypothyroidism induced by propylthiouracil decrease sirtuin1 content in rat heart. J Lab Precis Med. (2017) 2:67. doi:10.21037/jlpm.2017.08.03
145. Wang Y, Song J, Nishimura T, Tsirka SE, Holzmann S, Moll UM. MicroRNA-208a is a regulator of cardiac hypertrophy and conduction in pressure-overloaded adult hearts. J Clin Invest. (2015) 130:2772–86. doi:10.1172/JCI75004
146. Fang T, Xie S, Qiu S, Chen X, Wang X, Li Y, et al. The role of miR-21 in cardiac hypertrophy. PLoS ONE. (2016) 11:e0143075. doi:10.1371/journal.pone.0143075
145. Thakran S, Sharma P, Attia RR, Hori RT, Deng X, Elam MB, et al. Role of Sirtuin 1 in the regulation of hepatic gene expression by thyroid hormone. J Biol Chem. (2013) 288:807–18. doi: 10.1074/jbc.M112.435790

146. Suh JH, Sieglaflf DH, Zhang A, Xia X, Cвроor A, Wiminer GE, et al. SIRT1 is a direct coactivator of thyroid hormone receptor β1 with gene-specific actions. PLoS ONE. (2013) 8:e70097. doi: 10.1371/journal.pone.0070097

147. Singh BK, Sinha RA, Ohba K, Yen PM. Role of thyroid hormone in hepatic gene regulation, chromatin remodeling, and autophagy. Mol Cell Endocrinol. (2017) 458:160–8. doi: 10.1016/j.mce.2017.02.018

148. Rajamohan SB, Pillai VB, Gupta M, Sundaresan NR, Birukov KG, Samant S, et al. SIRT1 promotes cell survival under stress by deacetylation-dependent deactivation of poly(ADP-ribose) polymerase 1. Mol Cell Biol. (2009) 29:4116–29. doi: 10.1128/MCB.00121-09

149. Buguyei-Twum A, Ford C, Civitarese R, Seegobin J, Desjardins JF, et al. Sirtuin 1 activation attenuates cardiac fibrosis in a rodent pressure overload model by modifying Smad2/3 transactivation. Cardiovasc Res. (2018) 114:1629–41. doi: 10.1093/cvr/cvy131

150. Tanno M, Kuno A, Yano T, Miura T, Hisahara S, Ishikawa S, et al. Induction of manganese superoxide dismutase by nuclear translocation and activation of SIRT1 promotes cell survival in chronic heart failure. J Biol Chem. (2010) 285:8375–82. doi: 10.1074/jbc.M109.090266

151. de Lange P, Cioffi F, Senese R, Moreno M, Lombardi A, Silvestri E, et al. Sirtuin 1 activation attenuates cardiac fibrosis in a rodent pressure overload model by modifying Smad2/3 transactivation. Mol Cell Biol. (2017) 37:243–52. doi: 10.1161/CIRCHEARTFAILURE.108.0151413

152. de Lange P, Cioffi F, Senese R, Moreno M, Lombardi A, Silvestri E, et al. Sirtuin 1 activation attenuates cardiac fibrosis in a rodent pressure overload model by modifying Smad2/3 transactivation. Proc Natl Acad Sci U S A. (2017) 114:1629–41. doi: 10.1093/cvr/cvy131

153. Louzada RA, Carvalho DP. Similarities and differences in the peripheral actions of thyroid hormones and their metabolites. Front Endocrinol. (2018) 9:394. doi: 10.3389/fendo.2018.00394

154. Bianco AC, Kim BW. Deiodinases: implications of the local control of thyroid hormone action. J Clin Invest. (2006) 116:2571–9. doi: 10.1172/JCI29812

155. Bianco AC, Kim BS. Pathophysiological relevance of deiodinase polymorphism. Curr Opin Endocrinol Diabetes Obes. (2018) 25:341–6. doi: 10.1097/MED.0000000000000428

156. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on ‘adequate’ doses of L-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol. (2002) 57:577–85. doi: 10.1046/j.1365-2265.2002.01654.x

157. Walsh JP. Dissatisfaction with thyroxine therapy — could the patients be right? Curr Opin Pharmacol. (2002) 2:717–22. doi: 10.1016/S1474-4892(02)00299-6

158. Celi FS, Zemskova M, Linderman JD, Smith S, Drinkard B, Sachdev V, et al. Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind, crossover trial of liothyronine versus levothyroxine. J Clin Endocrinol Metab. (2011) 96:3466–74. doi: 10.1210/jc.2011-1329

159. Pantos C, Mourouzis I, Cokkinos DV. Thyroid hormone and cardiac repair/regeneration: from Prometheus myth to reality? Can J Physiol Pharmacol. (2012) 90:977–8. doi: 10.1139/y2012-031

160. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, et al. Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation. (2003) 107:708–13. doi: 10.1161/01.CIR.0000048124.64204.3F

161. Rajagopalan V, Zhang Y, Ojamaa K, Chen YF, Pingitore A, Pol CJ, et al. Safe oral triiodo-L-thyronine therapy protects from post-infarct cardiac dysfunction and arrhythmias without cardiovascular adverse effects. PLoS ONE. (2011) 6:e151413. doi: 10.1371/journal.pone.0151413

162. Pantos C, Mourouzis I, Markakis K, Dimopoulos A, Xinaris C, Cokkinos AD, et al. Thyroid hormone attenuates cardiac remodeling and improves hemodynamics early after acute myocardial infarction in rats. Eur J Cardiothorac Surg. (2007) 32:333–9. doi: 10.1016/j.ejcts.2007.05.004

163. Henderson KK, Danzi S, Paul JT, Leya G, Klein I, Samarel AM. Physiological replacement of T3 improves left ventricular function in an animal model of myocardial infarction-induced congestive heart failure. Circ Heart Fail. (2009) 2:243–52. doi: 10.1161/CIRCHEARTFAILURE.108.810747

164. Forini F, Lionetti V, Ardehali H, Pucci A, Cecchetti F, Ghanefar M, et al. Early long-term L-T3 replacement rescues mitochondria and prevents ischemic cardiomyopathy in rats. J Cell Mol Med. (2011) 15:514–24. doi: 10.1111/j.1582-4934.2010.01014.x

165. Barile L, Lionetti V, Cervio E, Matteucci M, Torelli M, Pitti L, Lionetti V. Barley beta-glucan promotes MnSOD expression and enhances angiogenesis under oxidative microenvironment. J Cell Mol Med. (2015) 19:227–38. doi: 10.1111/jcm.12442

166. Pantos C, Mourouzis I, Xia N, Panagiotou M, Cokkinos DV. Low-term thyroid hormone administration re-shapes left ventricular chamber and improves cardiac function after myocardial infarction in rats. Basic Res Cardiol. (2008) 103:308–18. doi: 10.1007/s00395-008-0697-0

167. Agostini S, Chiavacci E, Matteucci M, Torelli M, Pitti L, Lionetti V. Beta-glucan promotes MnSOD expression and enhances angiogenesis under oxidative microenvironment. J Cell Mol Med. (2015) 19:227–38. doi: 10.1111/jcm.12442

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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