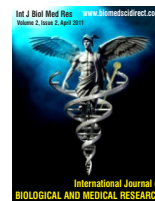


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Review Article

Interplay of Histone Acetylation and Transcription Factors in Cardiac Hypertrophy

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ABSTRACT

Adult cardiac disease is the most frequent cause of mortality in the western world where death, as a result of heart failure, is more prevalent than all disorders combined. Heart failure can be defined as a deficiency in the ability of the heart to pump an adequate supply of blood around the body which can be exemplified by cardiomyopathies. Hypertrophic Cardiomyopathy results due to pathological thickening of the heart muscles (sarcomeres replicate) /cardiac hypertrophy. Several (around 600) mutations have been identified in sarcomeric as well as other modifier genes that precipitate Hypertrophic cardiomyopathy. Our lab has also identified several novel mutations in the sarcomeric genes in the Indian population which could correlate to the epigenetics of the genes. Epigenetic changes like histone acetylation and DNA methylation are transient and involves no base changes. Recently, multiple transcriptional pathways have been identified involved in cardiac hypertrophy along with epigenetic modifications. Here we have tried to concentrate upon the role of histone acetylation and associated transcription factors in cardiac hypertrophy with respect to Hypertrophic Cardiomyopathy for the identification of therapeutic targets in molecular pathways. We hypothesise that apart from the pathways reviewed below, several others are yet to be unearthed for a greater understanding. Of special interest is the fact that reactivation of fetal genes leads to cardiac hypertrophy which is possible due to the interplay of transcription factors and histone acetyl transferase/histone deacetylases. Also, the pathways are highly complex since some classes of HDAC promote hypertrophy while others repress. Several therapeutic targets have been identified and many drugs against HCM are in variable stages of clinical trials with respect to histone deacetylases and transcription factors.

Keywords: Cardiac hypertrophy, cardiac fetal genes, transcription factors, histone acetylation/deacetylation

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1. Introduction

Cardiomyopathy, which literally means "heart muscle disease," is the deterioration of the function of the myocardium (i.e., the actual heart muscle). Hypertrophic cardiomyopathy (HCM) is a disease of the myocardium (the muscle of the heart) in which the myocardium is hypertrophied (thickened). The thickening of the cardiac muscle forces the heart to work harder to pump blood. This

condition is often associated with an abnormal heartbeat (arrhythmia) and can lead to heart failure and sudden death, especially among young athletes. The heart muscles thicken due to the replication of sarcomeres (contractile elements). It is frequently asymptomatic until sudden cardiac death. In addition, the normal alignment of muscle cells is disrupted, a phenomenon known as *myocardial disarray*.

1.1. Causes

Hypertrophic growth accompanies many forms of heart disease, including ischemic diseases, myocardial infarction, hypertension, aortic stenosis, and valvular dysfunctions. Although the initial hypertrophic responses seem to be an adaptation to those stimuli, the sustained stress may lead to cardiomyopathy

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and heart failure, a major cause of human morbidity and mortality. Cardiac hypertrophy is also induced by chemical inducers like isoproterenol/angiotensinII / phenylephrine(in presence of p300 and CBP) ,swimming , reactive oxygen species, TNF α , myotrophin, phenylephrine, endothelin-1, and angiotensin II.

Epigenetic modification of chromatin includes methylation of genomic DNA as well as acetylation, methylation, and phosphorylation of histone proteins. Such epigenetic changes play important roles in the regulation of gene transcriptional activity associated with cell growth and differentiation as well as with organ development [1-3]. In eukaryotes, histone-dependent packaging of genomic DNA into chromatin is a central mechanism for gene regulation. The basic unit of chromatin, the nucleosome, comprises DNA wrapped around a histone octamer. Nucleosomes interact to create a highly compact structure that limits access of transcriptional machinery to genomic DNA, thereby repressing gene expression [4]. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) act in an opposing manner to control the acetylation state of nucleosomal histones. Acetylation of the conserved amino-terminal histone tails by HATs is thought to relax nucleosomal structure by weakening the interaction of the positively charged histone tails with the negatively charged phosphate backbone of DNA, allowing access of transcriptional activators and gene induction. Histone deacetylases (HDACs) counteract HAT activity by catalyzing the removal of acetyl moieties from lysine residues in histone tails, thereby inducing chromatin condensation and transcriptional repression[5].It is becoming increasingly evident that histone deacetylases (HDACs) have a prominent role in the alteration of gene expression during the growth remodeling process of cardiac hypertrophy. HDACs are generally viewed as corepressors of gene expression.

This review tries to focus on the interaction of various transcription factors and HAT/HDACs that reactivate fetal genes; overexpress/repress other cardiac muscle genes and on the trials to treat cardiac hypertrophy.It looks into how several transcription factors act as central points onto which many molecular pathways converge.

2. Histone Deacetylases

Mammalian HDACs can be divided into four classes based on their sequence motifs and catalytic mechanisms [6,7]. Class I, II, and IV HDACs are evolutionarily related Zn⁺-dependent hydrolases. The members of class I (HDAC1, -2, -3, and -8) are expressed ubiquitously and consist mainly of a deacetylase domain are involved in hypertrophy , especially HDAC1&2. The role of Hdac3 has been less well explored. Whether Hdac3 participates in mediating the effects of HDAC inhibitors in the heart or plays an independent role in cardiac development, growth, and hypertrophic response is presently unknown. Interestingly, Hdac1 and Hdac2 display evidence of redundancy with regard to the regulation of cardiac development and morphogenesis; combined loss of Hdac1 and Hdac2 in cardiac myocytes results in complete perinatal lethality due to severe cardiac defects in excess of that seen in either individual knock-out [8].This may suggest a similar evolution pattern of *HDAC1& 2* genes to Hb genes / pseudogenes. The overlapping functions of Hdac1 and Hdac2 may be due, at least in part, to their co-existence within the same Sin3A, NuRD, and

CoREST co-repressor complexes [9,10]. Hdac3, which is structurally related to Hdac1 and Hdac2, is a component of the NCoR-SMRT co-repressor complex [11].

Class II HDACs (HDAC4, -5, -7, and -9) are highly expressed in muscle, brain, and T cells. They recruit Class I HDAC for deacetylation through MITR, a splicing variant of HDAC 9 [12]. Class II HDACs (HDAC4 and 5), are Ca/calmodulin-dependent kinase (CaMK)-responsive repressors of hypertrophic signaling stimulated by calcineurin .Class II HDAC levels do not appear to change in stressed myocardium [13,14]. Instead, these HDACs are shuttled from the nucleus to the cytoplasm in response to stress , which provides a posttranslational mechanism which will be discussed under MEF-2. HDAC11 is considered to be structurally diverse enough from the other Zn⁺-dependent HDACs to be classified as a separate class (class IV) [15]. Class III HDACs are related to the yeast HDAC, silent information regulator 2, and use nicotinamide adenine dinucleotide as a co-substrate [16].

It was suggested that different classes of HDACs suppress distinct sets of hypertrophic program-influencing genes. For example, class II HDACs suppress pro-hypertrophic genes, whereas class I HDACs might repress expression of anti-hypertrophic genes. There is evidence for a potential role of class I HDACs in cardiac growth, but the mechanism is still undefined and even less clear than for class II HDACs [17,18]. Forced overexpression of class II HDACs 5 or 9 in cardiac myocytes prevents hypertrophy in response to diverse agonists such as pressure overload or introduction of the calcineurin transgene [13,14,19,20]. Specific histone deacetylases (HDACs) can hence play a positive and negative role in determining cardiac myocyte size [21].

The HDAC targets identified in cardiomyocytes include several genes related to cell growth or differentiation that might play an important role in heart function. In addition to *Itpr3* and *Jag2*, such genes include those for G protein-coupled receptors (Senr, Gbl), regulators of cytosolic Ca²⁺ concentration (phosphodiesterase, Pik4cb, Pacsin1), and mediators of growth signaling (Ccmd1, Runx1, Fos11, Il11, Oct11, Sox6). These various genes are under epigenetic control in cardiomyocytes.

2.1.Histone acetylation and cyclin kinase inhibitors

The withdrawal of postnatal cardiomyocytes from the cell cycle is linked to significant down-regulation of cyclins, CDKs, and E2F transcription factors and to up-regulation of the negative regulators of cell cycle progression including FOX-1 dependent activation of Cdkn1a, Cdkn1b, Cdkn1c, and Cdkn2c [22,23]. Hdac3 overexpression in cardiac myocytes suppresses *Cdkn1a*, *Cdkn1b*, *Cdkn1c*, *Cdkn2b*, and *Cdkn2c* mRNA expression neonatal P1 hearts leading to increased cardiomyocyte hyperplasia without hypertrophy [24]. Absence of HDAC1 leads to elevated levels of CKI p21(WAF1/CIP1) & p27(KIP1) which is also observed when HDAC inhibitors are used.

3.Role Of Fetal Genes In Hypertrophy

Cardiac myocytes rapidly proliferate during embryonic and fetal life but generally lose their ability to proliferate shortly after birth [25]. The fetal genes that are re-expressed in hypertrophy are ANP (atrial natriuretic peptide) and BNP(brain natriuretic peptide).

3.1.REST

The transcriptional repressor REST [RE1 (repressor element 1)-silencing transcription factor] is a key factor in repressing the foetal cardiac gene programme in the adult heart [26,27]. Both the BNP and ANP genes contain an RE1-binding site for REST. Their promoters are repressed by REST which mediates transcriptional repression by recruiting co-repressor complexes that alter the post-translational modifications of the chromatin at the target gene promoter. An N-terminal repression domain in REST interacts with the mSin3A or mSin3B complexes, which repress transcription via their associated HDAC (histone deacetylase) activity (HDAC1 and HDAC2) [28,29]. A C-terminal repressor domain in REST interacts with the co-repressor CoREST, which is part of a complex containing HDACs (HDAC1 and HDAC2), a histone H3 K4 demethylase (LSD1) and an ATP-dependent chromatin remodelling enzyme (BRG1) [29,30]. There is some evidence suggesting that REST represses particular genes using different mechanisms in different cells. This indicates that not only is loss of REST repression sufficient for BNP and ANP re-expression but also that loss of REST repression alone is sufficient to drive hypertrophy. This suggests that REST is involved in pathways leading to hypertrophy.

3.2.NRSF

It was recently reported that a transcriptional repressor, neuron-restrictive silencer factor (NRSF), represses expression of fetal cardiac genes, including atrial and brain natriuretic peptide (ANP and BNP), by recruiting class II histone deacetylase (HDAC) and that attenuation of NRSF-mediated repression contributes to the reactivation of fetal gene expression during cardiac hypertrophy [31]. The molecular mechanism by which the activity of the NRSF-HDAC complex is inhibited in cardiac hypertrophy remains unresolved.

4.Transcription Factors

Several DNA-binding transcription factors have been shown to depend on HDAC activity. Cardiac hypertrophy is regulated by activation of heart-specific transcription factors such as GATA4, MEF2, and immediate early genes like c-jun and c-fos [32].

4.1.GATA

Six GATA transcription factors have been identified in vertebrates and parsed into two subclasses based on their expression patterns. GATA-1, -2, and -3 are prominently expressed in hematopoietic cell lineages while GATA-4, -5, and -6 are expressed in various mesoderm and endoderm derived tissues such as heart, liver, lung, gonad, and gut [33]. GATA4 is also expressed in the adult heart where it is thought to function as a key transcriptional regulator of numerous cardiac genes including atrial natriuretic factor (ANF), b-type natriuretic peptide (BNP), α -myosin heavy chain (α -MHC), β -myosin heavy chain (β -MHC), and many others [33,34]. A number of stimuli like pressure overload, isoproterenol, phenylephrine, endothelin-1, angiotensin II and phorbol esters that induce cardiac hypertrophy and/or heart failure are known to enhance GATA4 transcriptional activity through phosphorylation. Serine 105 in GATA4 serves as a key

convergence point in regulating the cardiac hypertrophic response. GATA4 is also subject to negative regulation by glycogen synthase kinase 3 β (GSK3 β)-mediated phosphorylation [35].

4.2.p300 and CBP

The most extensively studied HATs in muscle are p300 and the closely related coactivator, CREB-binding protein (CBP), which play critical roles in physiological and pathological growth of cardiac myocytes. p300 is a transcriptional co-activator as well as an acetyltransferase [36,37] that interacts with cardiac transcription factors like Mef2d and SRF. The GATA family of transcription factors are also transcriptionally coactivated by p300 [38,39]. Importantly, p300, and not CBP, is specifically required for cardiac development since deletion of p300 leads to heart failure and death at E9.5–11 while loss of CBP results in no cardiac abnormalities [40,41].

Hypertrophy in response to pressure overload is initiated by an increase in p300 levels, and that p300 is the primary driver of both adaptive and maladaptive phases of cardiac hypertrophy in vivo through direct effects on MEF2 acetylation [42]. The pro-hypertrophic effects of p300 did not require experimental activation of other growth signals, suggesting that p300 is independent or at least upstream of these signals and associated phosphorylation events [13,14,19,20,43,44]. This supports the view that p300 promotes hypertrophy upstream of HDAC signal-mediated nuclear export and degradation, which serve to further potentiate the effects of p300.

4.3.MEF 2

Superactivation of the MEF2 transcription factor leads to the development of cardiac pathology. MEF2 factors selectively associate with class II HDACs via an 18-amino-acid motif present only in these HDACs, resulting in repression of genes harboring MEF2 binding sites [43]. Stimulation of cardiomyocytes with neurohumoral agonists acting through G-protein coupled receptors (GPCRs) activates kinase pathways that culminate with the phosphorylation of class II HDACs and their export to the cytoplasm as a complex with 14-3-3 proteins. The nuclear export protein CRM1 is required for HDAC nuclear export. The release of class II HDACs from MEF2 allows for the association of HATs with MEF2 and consequentially chromatin relaxation and transcriptional activation of fetal cardiac genes. MEF2 does not directly program the adult hypertrophic growth program, but instead appears to regulate cardiac dilation and the addition of sarcomeres in series.

As a consequence of an increase in intracellular calcium concentration, the Ca²⁺/CaM complex associates with class II HDACs (HDAC4 and -5 have a CaM-binding motif within the MEF2-binding regions [45]), thereby displacing MEF2 and providing a signal in addition to HDAC phosphorylation to derepress MEF2 target genes and CaM also competes with MEF2 for binding to Cabin1, resulting in the dissociation of MEF2 from its repressor Cabin1 and, consequently, in MEF2 activation [46]. Cabin1 docks on the same region of MEF2 as class II HDACs and represses MEF2 activity by (1) recruiting the mSin3 corepressor and class I HDACs to MEF2 target genes and (2) by displacing p300 and NFAT from

MEF2 [47]. Two other MEF-2 activation mechanisms are (a) MEF2 is directly phosphorylated by BMK1, which is downstream of and activated by MEK5 [48,49]. (b) Calcineurin dephosphorylates NFAT which translocates to the nucleus and facilitates recruitment of HATs to MEF-2 response elements [50].

4.4. Gsk3 β

Resistance to hypertrophy was associated with increased expression of the gene encoding inositol polyphosphate-5-phosphatase f (Inpp5f) resulting in constitutive activation of glycogen synthase kinase 3 β (Gsk3 β) via inactivation of thymoma viral proto-oncogene (Akt) and 3-phosphoinositide-dependent protein kinase-1 (Pdk1) and downregulation of Hdac2 since Gsk3 β is inactivated in presence of Hdac2. Hence Hdac2 and Gsk3 β are components of a regulatory pathway providing an attractive therapeutic target for the treatment of cardiac hypertrophy and heart failure [51].

4.5. NFAT

NFAT factors are critical regulators of several aspects of cardiac development and myocyte maturation. The calcium/calmodulin-activated protein phosphatase calcineurin (PP2B) and its downstream transcriptional effector NFAT have been implicated as critical transducers of the cardiac hypertrophic response. In response to elevated intracellular calcium like cytosolic Ca²⁺ transients, rather than localized perinuclear or nuclear Ca²⁺ signals, calcineurin becomes activated in the cytoplasm where it binds to NFAT and directly dephosphorylates the N-terminal regulatory domains, exposing a nuclear localization signal permitting its translocation to the nucleus and interaction with GATA4 as a means of inducing hypertrophic gene expression [16]. The idea that calcineurin (and NFAT) is primarily involved in cardiac hypertrophy in humans, however, is not shared by all investigators in the field, and this remains a hot topic of debate. NFAT factors function as a signaling convergence point whereby multiple stress/mitogen-activated pathways modulate transcriptional activity.

4.6. SRF and Hop

SRF is important for embryonic heart development and is a regulator of the hypertrophic growth response in the adult heart. SRF interacts with SMAD1/3, Nkx2-5, and GATA4 to synergistically activate muscle gene expression and induce HCM [52-59]. Myocardin, is a SAP domain-containing nuclear factor [60,61]. Myocardin-related transcription factors (MRTF) A and B have also been shown to interact with SRF [62]. Homeodomain-only protein (Hop) is specific to the heart and is a nuclear protein that does not bind DNA. Hop-dependent genes contain binding sites for serum response factor (SRF). Hop binds SRF, inhibits SRF-dependent gene expression, and interferes with the cooperation of SRF with its coactivator myocardin [63,64] by recruiting an HDAC 2 to SRF [65] and Hop prevents the ability of myocardin to cause histone acetylation.

4.7. Hsp70

The heart reacts to protect itself from stresses like ischemia and heat, by increasing the antiapoptotic cascades such as AKT

signaling, [66] leading to forced expression of Hsp70, which coincides well with the activation of Hdac2. Hypertrophic stimuli induces the expression of heat shock protein (Hsp)70 and activation of HDAC2 preceded substantial hypertrophic events, implying that activation of HDAC2 is not a result but a cause of hypertrophy.

4.8. NF κ B

Nuclear Factor κ B (NF κ B) is a transcription factor that can regulate the expression of immediate early and stress-response genes in diverse cell types. NF κ B is regulated by a cytoplasmic inhibitory protein known as I κ B, which is phosphorylated by I κ B kinase- α (IKK α) and/or β leading to the ubiquitination and degradation of I κ B, permitting NF κ B nuclear translocation [67]. Upstream, IKK activity is regulated by NF- κ B-inducing kinase (NIK), which itself is stimulated by a complex that is located within the tumor necrosis factor- α (TNF α) receptor. NF κ B has also been implicated as a necessary and sufficient regulator of cardiac hypertrophy. Inhibition of NF κ B attenuates the initial hypertrophy.

4.8.1. Nkx2-5

The homeobox transcription factor Nkx2-5 (also known as Csx) is highly expressed in early heart progenitor cells as they commit to the cardiac lineage during embryogenesis, where it continues to be expressed in the heart throughout adulthood [68-71]. Nkx2-5 participates in the cardiac hypertrophic response given the observation that its expression is upregulated during pressure overload or stress stimulation. It interacts with other cardiac transcription factors such as GATA4 and SRF, calmodulin binding transactivator (CAMTA), which itself promotes cardiomyocyte hypertrophy and activates ANF gene expression [72]. It functions as a modulator of the adult cardiac hypertrophic response.

4.9. Ncx1

Class I and class II HDACs play an important role in the basal expression and up-regulation of the sodium calcium exchanger (Ncx1) gene in adult cardiomyocytes [73]. Nkx2.5 interacts with transcriptional activator p300, which is recruited to the Ncx1 promoter. When Nkx2.5 is acetylated, it is found associated with HDAC5 whose overexpression stimulates Ncx-1 protein [73]. Notably, TSA treatment prevents p300 from being recruited to the endogenous Ncx1 promoter, resulting in the repression of Ncx1 expression.

4.10. TGF- β

Diverse members of the TGF- β superfamily elicit different signaling responses in the adult myocardium. TGF-beta is thought to be a pro-hypertrophic cytokine in the heart. Independent of Smad proteins, TGF- β can also elicit signals through the MAPK cascade that includes TGF- β activated kinase 1 [74].

4.11. Smad

Smad transcription factors primarily function as inducible regulators of transforming growth factor- β (TGF- β) superfamily member signals. Activation of Smad proteins downstream of specific ligands appears to function in an anti-hypertrophic capacity. In support of this hypothesis, the TGF- β family member growth-differentiation factor 15 (GDF-15) was shown to also

function as an anti-hypertrophic regulatory factor in the adult heart in association with Smad2/3 activation [75,76]. Also, elevated levels of Rgs5 protein blocks MEK-ERK1/2 activation leading to significant inhibition, whereas activation of MEK-ERK1/2 resulted in up-regulation of collagen synthesis and Smad 2/3 signaling [76].

4.12.Sp

The Sp family of transcription factors is important in the assembly of the basal transcriptional machinery, potentially acting as a central and widespread regulatory network in pathologic hypertrophy. It has been previously shown that Sp1 and Sp3 have counter regulatory functions in avian myocytes [77]. Although Sp3 expression is downregulated during pathologic hypertrophy, we have found that Sp3-associated HAT activity is increased and HDAC activity is significantly decreased. Hence, acetylation of Sp3 may convert it from a repressor to a transcriptional activator during the induction of pathologic cardiac hypertrophy and heart failure [77].

4.13.Hand1/2

The expression of Hand1 is predominantly in the left ventricle and is excluded from the right ventricle. In contrast, the expression of Hand2 is restricted to the right ventricle. With respect to the adult heart, very little direct evidence exists to implicate a role for Hand1 or Hand2 in acquired pathological conditions. Correlative evidence has shown that Hand1, but not Hand2, is downregulated in cardiomyopathic hearts from human patients [78]. However, in a rat model of pressure overload, Hand2 was reported to be upregulated in the right ventricle [79].

Thus changes in myocardial Hand activity may regulate/modulate adult heart disease responses.

4.14.Egr-1

Early growth response-1 (Egr-1) was identified as an immediate early response gene [80]. Egr-1 can bind either a GC-rich element (TGCGGGGGCG) that overlaps with the binding site for Sp1, or an element comprised of the sequence TCCTCCTCCTCC. Absence of Egr-1 reduced cardiac hypertrophy to isoproterenol and phenylephrine stimulation [81]. NGF1-A binding protein 1 (Nab1) overexpression inhibited pathologic cardiac hypertrophy, by directly inhibiting Egr-1 [82]. Thus, Egr-1 functions as yet another inducible factor to the array of adult cardiac growth regulators.

4.15.CREB

cAMP-response element (CRE) binding protein (CREB) is a 43 kDa basic leucine zipper (bZip) transcription factor that binds to the consensus sequence of TGANNTCA in association with other members of the CREB/ATF and AP-1 family [83-87]. It binds to CBP on being phosphorylated by protein kinase A, CAMK, cGmp which are activated by Ras protein.

Thus, the increase in sarcomeric proteins and induction of embryonic cardiac genes seen during pathologic hypertrophy are preceded and regulated by increase in myocardial transactivators, decreases in cardiac gene repressors, and induction of posttranslational modifications that modulate transcription factor function. Thus, the entire pathway can lead to either cardiac hypertrophy or resistance to hypertrophy (Refer to Flowchart 1 and Table-1).

FLOWCHART -1

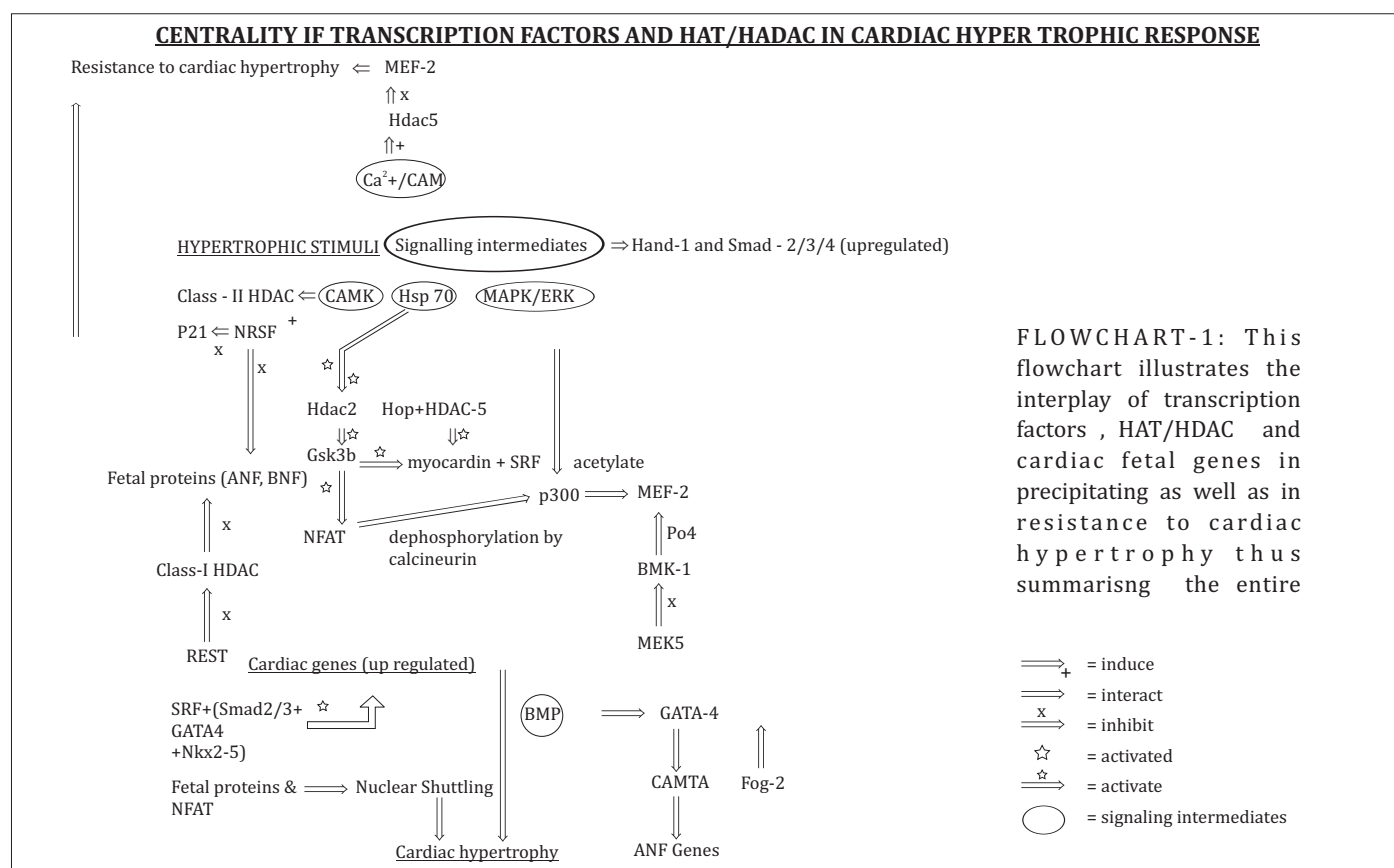


Table 1: A list of transcription factors and HAT/HDAC involved in up-regulation/downregulation of hypertrophy.

Transcription factors and HDAC/HAT that reduce hypertrophy	Transcription factors and HDAC/HAT that promote hypertrophy
Class-II HDAC	Class-I HDAC and Hdac-3
REST, NRSF	CAMTA,Nkx2-5
NGF1-A binding protein	ANF,BNF
Smad 2/3 +GDF-15	Egr-1
Cabin-1	TGF- β
Cyclin kinase inhibitor-p21	Calcineurin and NFAT

5. Treatment

Since several molecular pathways involving HDAC and transcription factors have been identified and characterized, there is a huge prospective commercial market for novel drugs targeted towards them to treat cardiac hypertrophy. Several chemical inhibitors of HDACs have been identified, including trichostatin A (TSA), sodium butyrate, and HC-toxin which utilize MITR, a splicing variant of HDAC9 that has only the N-terminal of Class-II HDAC to repress MEF-2. But they are non-selective in action. By contrast, the bicyclic tetrapeptide HDAC inhibitors FK228 and Spiruchostatin A appear to possess selectivity towards class I HDACs [88 and unpublished data].

HDAC inhibitors are in phase I, II, and III clinical trials for hematological and oncological conditions [89,90]. Recently, suberoylanilide hydroxamic acid (also referred to as vorinostat/Zolinza) was approved by the Food and Drug Administration for the treatment of cutaneous T cell lymphoma [91].

The apicidin derivative, API-D, is capable of reducing hypertrophy. Therapeutic agents that are able to counteract the loss of REST function and blunt the hypertrophic response mediated by p300 could reduce that risk without compromising short-term adaptation. Indeed, curcumin, a polyphenolic compound reported to have antioxidant, antifumor and anti-histone acetyltransferase activity, was recently shown to blunt hypertrophy [92-94].

Elucidation of the specific functions of individual HDACs will be important to determine the molecular targets of these inhibitors and to provide information relevant to understanding and preventing potential cardiac side effects.

6. Conclusion

Dissection and characterization of the signaling pathways leading to cardiac hypertrophy has led to a wealth of knowledge about this condition both physiological and pathological. Although these pathways have still to be defined further, there will undoubtedly be future pathways and players to be discovered like,

whether REST is involved in pathways leading to hypertrophy. A new revelation is that the re-activation of fetal genes leads to cardiac hypertrophy via HAT/HDAC and transcription factors interplay. The challenge currently will be to translate this scientific knowledge and understanding into potential pharmacological therapies for the treatment of pathological cardiac hypertrophy. Consequently, the emerging picture is that, although distinct hypertrophic and developmental stimuli appear to converge on common transcription factors such as GATA4 and SRF, activation of these factors does not result in indiscriminate expression of GATA4 or SRF-dependent genes. Simultaneous activation of cofactors is required but, in addition, there are many indications that one or more additional levels of regulation exist that allow a cell to further distinguish between different stimuli. Also, there is a need to understand the role of HDAC Class-I & II clearly since they seem to repress/ induce hypertrophy in different pathways and we suggest that there may be a similar evolution pattern of *Hdac 1& 2* genes to Hb genes / pseudogenes.

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