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Medicine in focus

Heart failure: The pivotal role of histone deacetylases

Ruth Hewitson[a], James Dargan[a], David Collis[a], Aneta Green[a], Narain Moorjani[b], Sunil Ohri[b], Paul A. Townsend[c,*]

[a] Cancer Sciences, Faculty of Medicine, Southampton General Hospital, University of Southampton, Southampton SO16 6YD, UK
[b] Wessex Cardiac Centre, Southampton General Hospital, University of Southampton, Southampton SO16 6YD, UK
[c] Faculty Institute for Cancer Sciences, University of Manchester, Manchester Academic Health Science Centre, Research Floor, St Mary's Hospital, Oxford Road, Manchester, M13 9WL, UK

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ABSTRACT

Heart failure, a state in which cardiac output is unable to meet the metabolic demands of the tissues, poses a significant health burden; following an initial hospital admission with heart failure, five-year mortality is close to 50%. Cardiac hypertrophy, characterised by increased cardiomyocyte size and protein synthesis, has deleterious effects when prolonged and contributes to heart failure. Cardiac hypertrophy itself increases risk of morbidity and mortality.

Histone deacetylases are chromatin modifiers which deacetylate the N-terminal tails of histones and have been implicated in common cardiac pathologies associated with hypertrophy. There are 18 histone deacetylases separated into four classes. Class I histone deacetylases interact with heat shock proteins and are pro-hypertrophic, class IIa histone deacetylases repress hypertrophy by inhibiting the activity of transcription factors such as myocyte enhancer factor 2. Histone deacetylases present an exciting new target in combating cardiac hypertrophy and progression to heart failure.

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Key facts

- Cardiac hypertrophy is characterised by increased cardiomyocyte size and protein synthesis and contributes to the development of heart failure, which increases morbidity and mortality.
- The chromatin modifiers, histone deacetylases (HDACs), exert both pro- and anti-hypertrophic effects on the heart.
- Class I histone deacetylases, which interact with heat shock proteins, are pro-hypertrophic. Class IIa histone deacetylases inhibit the activity of transcription factors such as myocyte enhancer factor 2 and repress hypertrophy.
- Many HDAC targets are transcription factors that act on the cell cycle; HDAC inhibitor (HDACi) species are used successfully in the treatment of cutaneous T-cell lymphoma and rheumatoid arthritis. Due to involvement of HDACs in cardiac hypertrophy via multiple pathways, HDACis may offer therapeutic benefit in heart disease.

1. Introduction: heart failure

1.1. The burden of heart failure

Cardiovascular disease remains the number one cause of mortality worldwide (World Health Organisation, 2012). Common pathologies such as hypertension, ischaemic heart disease and valvular heart disease can ultimately lead to heart failure, a state in which cardiac output is unable to meet the metabolic demands of the tissues. Following an initial hospital admission with heart failure, five-year mortality is close to 50%, highlighting the requirement for more effective strategies to combat heart disease (Lloyd-Jones et al., 2009). Fundamental to heart failure is cardiac remodelling characterised by hypertrophy, cell death and fibrosis (Kee and Kook, 2011). Such events are a consequence of cellular changes that commonly involve the reactivation of foetal genes with consequent cardiac growth and repression of calcium-handling and cardiac contractile proteins (Barry and Townsend, 2010). As many signalling pathways lead to the remodelling integral to heart failure, new therapeutic strategies aim to target the downstream mediators, where many of these pathways converge (McKinsey, 2012).

1.2. The role of hypertrophy in heart failure

Cardiac hypertrophy, an initial adaptive response to increased pathological stress of the heart, has deleterious effects when

* Corresponding author. Tel.: +44 (0)161 701 6923; fax: +44 (0)161 701 6919.
E-mail address: paul.townsend-2@manchester.ac.uk (P.A. Townsend).

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prolonged and contributes to heart failure (Barry and Townsend, 2010). Characterised by increased cardiomyocyte size, protein synthesis and organisation of the sarcomere, hypertrophy is associated with volume and pressure overload states, myocardial infarction, cardiomyopathies and myocarditis (Kee and Kook, 2011). Though the heart enlarges to compensate for increased demand, the cardiomyocytes are structurally and functionally inadequate to accommodate these changes leading to loss of cardiomyocytes via apoptosis or necrosis with subsequent fibrosis. In contrast, physiological cardiac hypertrophy, witnessed in pregnant women and athletes, is associated with normal cardiac structure. Cardiomyocyte hypertrophy and enhanced sarcomere synthesis without pathological remodelling permits normal or enhanced cardiac function (McMullen and Jennings, 2007).

In pathological hypertrophy, impaired contraction leads to a reduced ejection fraction during systole and impaired relaxation results in inadequate filling during diastole. Thus, cardiomyocyte death poses further stress on the heart, perpetuating the deleterious cycle with progression to cardiac failure (Green et al., 2012). Hypertrophy itself also increases risk of morbidity and mortality and as such represents a significant target in limiting the progression of heart disease (Vakili et al., 2001).

2. Pathogenesis: mechanisms of hypertrophy

2.1. Transcriptional regulation of hypertrophy

Nuclear factor of activated T cells (NFAT), GATA, serum response factor (SRF), calmodulin-binding transcription factor (CAMTA) and myocyte enhancing factor 2 (MEF2) are master regulators common to most hypertrophic pathways (Barry and Townsend, 2010; Davis et al., 2003; Song et al., 2006). MEF2, a MADS-box transcription factor, is potently pro-hypertrophic and drives expression of several cardiac genes including atrial natriuretic peptide (ANP) and troponins (Barry and Townsend, 2010). In pressure overload models, reduced expression of MEF2D decreases left ventricular dilation, myocyte hypertrophy and fibrosis whereas over-expression induces severe cardiac hypertrophy (Kim et al., 2008).

Many signals integrate to induce activation of MEF2 including those from MAPKs and calcium handling; one major mechanism of regulation is the epigenetic control of MEF2 by chromatin modifiers. In particular, the proteins governing acetyvlation status of histones appear most significant in MEF2-related hypertrophic changes (Barry and Townsend, 2010).

2.2. Chromatin modification

Histones are subject to post-translational modifications owing to long N-terminal tails (Kee and Kook, 2011); acetylation status is central to gene expression and is controlled by two opposing protein families; histone acetyl transferases (HATs) and HDACs. The former acetylates lysine residues on histones, relaxing chromatin structure and permitting access of transcription factors to DNA.

HDACs, the opposing regulators of histone acetylation, remove acetyl groups from lysine residues and have been implicated in a variety of cardiac diseases including arrhythmias, acute coronary syndromes and heart failure. They have been demonstrated to play a role in autophagy, fibrosis, contractility and energy metabolism and influence both the development and repression of cardiac hypertrophy (McKinsey, 2012).

2.3. Histone deacetylases (HDACs)

There are 18 HDACs divided into four subclasses: class I HDACs (HDAC1, 2, 3 and 8) are nuclear proteins ubiquitously expressed in cells, whereas classes II and IV HDACs are found in both the cytoplasm and nucleus and are more tissue specific. Class III HDACs, more commonly known as sirtuins, are known to exist in the nucleus, cytoplasm and mitochondria of the cell. Class II HDACs are further divided into two groups: IIa (HDAC4, 5, 7 and 9) and IIb (HDAC6 and 10). Evidence from murine models demonstrates that classes I and IIa HDACs are pro- and anti-hypertrophic respectively via distinct molecular pathways, and that both can play a potentially significant role in cardiovascular disease (Kee and Kook, 2011).

2.3.1. Class I HDACs

A significant body of evidence implicates class I HDACs in cardiac cell growth and proliferation, pathological hypertrophy, ischaemic heart disease and arrhythmia. Embryonic lethality is witnessed in HDAC1 deficient mice due to cardiac proliferation defects (Lagger et al., 2002) and HDAC2 deficient mice initially appeared to be resistant to hypertrophic stimuli using a gene trap technique (Trivedi et al., 2007). However, the results were disputed by Montgomery et al. (2007) who demonstrated a conditional knock-out of cardiac HDAC2 was insufficient to block hypertrophy. The latter also indicated that global deletion of HDACs 1 or 2 cause embryologic or perinatal mortality. Suggesting that the LacZ insertion lines of Trivedi et al. (2007) were creating a hypomorphic allele rather than a true null, the remaining levels of HDAC2 were sufficient for murine viability. Montgomery et al. also showed that there was no phenotype associated with a single cardiac specific HDAC knockout (Montgomery et al., 2007). This suggests a greater role for class I HDACs in non-cardiac specific progression of hypertrophy.

HDAC3 suppresses hypertrophy while enhancing proliferation; mice over-expressing HDAC3 have ventricular and septal thickening at neonatal day 1 but at 2 months do not have an increased proliferation index (Trivedi et al., 2008).

Recently, HDAC1 presence has been demonstrated on sarcomeres in hypertrophied cardiomyocytes. This could contribute to a reduction in cardiac contraction following deacetylation of sarcomeric proteins and loss of molecular regulation (Green et al., 2012).

2.3.2. The pro-hypertrophic mechanism of HDAC2

In response to hypertrophic stresses it has been found that HSP70 activates HDAC2 with subsequent hypertrophy. Conversely, HSP70 knock-out mice do not recruit HDAC2 and hypertrophy is reduced (Kee et al., 2008). Therefore the interaction between HDAC2 and HSP70 appears critical in the pro-hypertrophic signalling cascade.

An important downstream target of HDAC2 is Inpp5f which mediates cardiac hypertrophy via the phosphatidylinoditol 3-kinase (PI3 K) Akt-Gsk3β pathway. HDAC2 levels augmented by HSP70 reduce Inpp5f expression causing a build-up of inositol-3,4,5-triphosphate (PIP_3). Accumulated PIP_3 activates Akt which suppresses Gsk3β, relieving pro-hypertrophic pathways like β-catenin from inhibition (Trivedi et al., 2008). Inpp5f knock-out mice have a greater hypertrophic response and mice over-expressing Inpp5f are resistant to hypertrophy (Zhu et al., 2009).

Enzymatic activation of HDAC2 precedes hypertrophy in response to hypertrophic stimuli, and hypertrophy is not observed with mutant HDAC2 (Kee et al., 2008). However, certain HDACs regulate hypertrophy independent of catalytic activity. A splice variant of HDAC9, MEF2 interacting transcription repressor (MITR), has anti-hypertrophic potential but lacks the deacetylase domain suggesting that its existence alone is effective in this role (Kee and Kook, 2011).

2.3.3. Class IIa HDACs

There is much evidence in the literature highlighting class IIa HDACs as negative regulators of hypertrophy in cardiac disease. HDAC5 knockout mice develop hypertrophy in response to

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