EBioMedicine 40 (2019) 21–22

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

HDAC inhibitors and cardioprotection: Homing in on a mechanism of action

Kate L. Weeks [a,b,*]

[a] Baker Heart and Diabetes Institute, Melbourne, VIC 3004, Australia
[b] Department of Diabetes, Central Clinical School, Monash University, Clayton, VIC 3800, Australia

Histone deacetylases (HDACs) are epigenetic regulators with important roles in numerous cellular processes. The HDAC superfamily is divided into four classes based on function and sequence similarity. The zinc-dependent class I, II and IV HDACs have been implicated in a range of processes relevant to cardiovascular diseases, including cardiac hypertrophy, fibrosis, calcium handling and inflammation [1]. Over the past decade, several groups have demonstrated that HDAC inhibitors (HDACi), such as the pan-HDACi suberoylanilide hydroxamic acid (SAHA), can reduce infarct size and attenuate pathological cardiac remodelling in rodent and rabbit models of myocardial infarction (MI) and ischemia/reperfusion injury (see Table 1 in [2] for summary). Current research focuses on elucidating the mechanisms by which HDACs contribute to cardiac remodelling and dysfunction, with the hope that more targeted approaches or the development of isoform-selective HDACi may provide a more favourable therapeutic index than pan-HDACi for the treatment of cardiovascular and metabolic diseases.

In this article of *EBioMedicine*, Tian and colleagues [3] identify one of the mechanisms by which valproic acid (VPA), a branched short-chain fatty acid that weakly inhibits both class I and class IIa HDACs [4], may provide protection in a setting of myocardial infarction (MI). VPA is routinely used in the treatment of epilepsy and bipolar disorder [5], and daily administration of VPA has previously been shown to attenuate pathological cardiac remodelling in an experimental model of MI [6]. In the current study, rats were subjected to 60 min of myocardial ischemia induced by occlusion of the left descending coronary artery (LAD) and dissected 24 h after the onset of reperfusion. VPA (250 mg/kg) was administered intraperitoneally upon LAD occlusion or at the time of reperfusion, as well as 12 h post-LAD ligation. VPA reduced infarct size, improved left ventricular ejection fraction, and attenuated markers of apoptosis, oxidative stress and myocardial injury. Improved systolic function and smaller infarct size were also observed in a group of animals that received VPA twice daily for 4 weeks post-MI.

To identify possible mechanisms by which VPA provided cardioprotection in this model, RNA-Seq was performed on left ventricular tissue from sham- and MI-operated rats, with and without VPA treatment. Consistent with the observed reductions in apoptotic, oxidative stress and myocardial injury markers, VPA treatment attenuated the expression of genes involved in cell death and inflammation, and dampened the downregulation of genes involved in oxidation reduction processes, metabolism and cardiac muscle contraction. Ingenuity Pathway Analysis identified the transcription factor forkhead box protein M1 (Foxm1) as a potential regulator of VPA target genes.

Foxm1 is a transcription factor that is expressed in cardiomyocytes during embryogenesis and downregulated in the adult heart [7]. Foxm1 is re-expressed following injury in a number of organs [7], but has not previously been examined in the context of myocardial injury. In the current study, cardiac protein levels of Foxm1 increased after MI, and were further increased by VPA treatment. The acetylation status of H3K27, an epigenetic mark associated with transcriptional activation, was increased within the Foxm1 promoter region of VPA-treated animals, providing a potential mechanism by which VPA could lead to increased Foxm1 expression.

To investigate whether Foxm1 signalling was responsible for the cardioprotective effects of VPA treatment, the authors used complementary gain- and loss-of-function approaches. In mice, administration of an adeno-associated viral vector (AAV) to increase expression of Foxm1 exclusively in cardiomyocytes (AAV serotype 9 in combination with a cardiac troponin T promoter) improved ejection fraction and reduced infarct size following permanent occlusion of the LAD. Conversely, in rats subjected to MI, treatment with the Foxm1 inhibitor thiostrepton completely abolished the protective effects of VPA treatment on infarct size and systolic function, indicating that Foxm1 signalling is required for the cardioprotective effects of VPA in this setting. This study did not directly compare AAV delivery of Foxm1 with VPA treatment in the mouse model of MI, therefore it is not possible to determine whether increasing expression of Foxm1 exclusively in cardiomyocytes was able to fully recapitulate the protective effects of VPA treatment. Foxm1 in other cardiac cell types may contribute to VPA-mediated cardioprotection. Indeed, in a transcriptional profiling study of different cardiac cell populations from infarcted and non-infarcted mouse hearts, MI upregulated the expression of Foxm1 in multiple cell types, including cardiomyocytes, fibroblasts, vascular endothelial cells and leukocytes [8]. Thus, investigation of the role of Foxm1 signalling in non-myocyte cardiac cell types during MI-induced injury and cardiac remodelling is warranted.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.12.003.
* Corresponding author at: Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne, VIC 3004, Australia.
E-mail address: kate.weeks@baker.edu.au.

https://doi.org/10.1016/j.ebiom.2019.01.015

Currently, four HDACi have been approved by the United States Food and Drug Administration for the treatment of haematological cancers (Romidepsin, Vorinostat, Panobinostat and Belinostat). Whether any of these HDACi or VPA can be repurposed for the treatment of cardiovascular diseases remains an ongoing area of research. Epidemiological studies of epileptic patients suggest that VPA may reduce the risk of MI [9,10], however this hypothesis is yet to be tested in clinical trials. The current study highlights the power of gene profiling technologies to identify mechanisms of action of therapeutic agents, and the importance of basic research to unravel the complex signalling pathways involved in post-infarct remodelling and the fibrotic response. The role of Foxm1 in cardiac biology has not been studied in detail. The generation of cell-type-specific loss- and gain-of-function mouse models will provide insight into the function of Foxm1 in the mammalian heart, and may lead to the development of more targeted therapies for the treatment of MI and other cardiovascular diseases.

Declaration of interests

Dr. Weeks has nothing to disclose.

Author contributions

Dr. Weeks wrote the manuscript.

Acknowledgements

Dr. Weeks is supported by an Emerging Leader Fellowship from The Shine On Foundation and the Baker Heart and Diabetes Institute.

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