Redox Biology 17 (2018) 440–449

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Cardiac-specific overexpression of aldehyde dehydrogenase 2 exacerbates cardiac remodeling in response to pressure overload

Sujith Dassanayaka[a,b], Yuting Zheng[a,b], Andrew A. Gibb[a,b], Timothy D. Cummins[c], Lindsey A. McNally[a,b], Kenneth R. Brittian[a,b], Ganapathy Jagatheesan[a,b], Timothy N. Audam[a,b], Bethany W. Long[a,b], Robert E. Brainard[d], Steven P. Jones[a,b], Bradford G. Hill[a,b,*]

[a] Institute of Molecular Cardiology, University of Louisville, Louisville, KY, United States
[b] Diabetes and Obesity Center, Division of Cardiovascular Medicine, University of Louisville, Louisville, KY, United States
[c] Division of Nephrology and Hypertension, Department of Medicine, University of Louisville, Louisville, KY, United States
[d] Department of Physiology, University of Louisville, Louisville, KY, United States

ARTICLE INFO

Keywords:
Heart failure
Hypertrophy
Oxidative stress
Aldehydes
Cardiac remodeling
Hormesis

ABSTRACT

Pathological cardiac remodeling during heart failure is associated with higher levels of lipid peroxidation products and lower abundance of several aldehyde detoxification enzymes, including aldehyde dehydrogenase 2 (ALDH2). An emerging idea that could explain these findings concerns the role of electrophilic species in redox signaling, which may be important for adaptive responses to stress or injury. The purpose of this study was to determine whether genetically increasing ALDH2 activity affects pressure overload-induced cardiac dysfunction. Mice subjected to transverse aortic constriction (TAC) for 12 weeks developed myocardial hypertrophy and cardiac dysfunction, which were associated with diminished ALDH2 expression and activity. Cardiac-specific expression of the human ALDH2 gene in mice augmented myocardial ALDH2 activity but did not improve cardiac function in response to pressure overload. After 12 weeks of TAC, ALDH2 transgenic mice had larger hearts than their wild-type littermates and lower capillary density. These findings show that overexpression of ALDH2 augments the hypertrophic response to pressure overload and imply that downregulation of ALDH2 may be an adaptive response to certain forms of cardiac pathology.

1. Introduction

Heart failure is associated with lipid peroxidation and the accumulation of α, β-unsaturated aldehydes [1,2], which react avidly with cellular nucleophiles and can propagate or amplify tissue injury [3]. Although the heart possesses several aldehyde-detoxifying enzymes [4,5], its capacity to remove aldehydes is diminished in heart failure. For example, aldose reductase, which reduces reactive aldehydes such as 4-hydroxynonenal (HNE) to relatively inert alcohols, is downregulated in the failing mouse heart [6], and glutathione-*S*-transferase activity, which conjugates aldehydes to glutathione, is lower in the pressure-overloaded rat heart [7]. Furthermore, the activity or abundance of aldehyde dehydrogenase 2 (ALDH2)—responsible for the majority of HNE detoxification in the heart [4,5]—is diminished in ischemia [4], after myocardial infarction [8,9], and in pressure overload-induced hypertrophy [10].

Although several studies indicate that ALDH2 protects the heart from injury and maladaptive remodeling (reviewed in [11–13]), accumulating evidence indicates that deficiency of the enzyme could be protective as well. For example, mice expressing the defective *Aldh2*2* mutation show lower aldehyde detoxification capacity yet are protected against ischemia-reperfusion injury [14]. Moreover, overexpression of ALDH2 worsens aging-induced cardiac hypertrophy and dysfunction and shortens lifespan [15,16], and deficiency of ALDH2 prevents cardiac hypertrophy caused by pressure overload [17]. These studies suggest that diminishment of mitochondrial aldehyde dehydrogenase capacity may actually confer beneficial consequences, redolent of the hormetic effects of mitochondrial reactive species on survival and longevity [18–20] and the critical role of oxidants in tissue adaptation to injury [21]. Nevertheless, it remains unclear whether the decrease in ALDH2 activity occurring in heart failure is deleterious or adaptive.

In this study, we examined whether cardiac-specific overexpression of ALDH2 influences cardiac remodeling in the context of pressure overload. Our data indicate that ALDH2 expression and activity are lower in the pressure-overloaded heart and that overexpression of ALDH2 augments hypertrophic responses and limits capillary density

* Correspondence to: Diabetes and Obesity Center, Department of Cardiovascular Medicine, University of Louisville, 580 S. Preston St., Rm 321E, Louisville, KY 40202, United States.
E-mail address: bradford.hill@louisville.edu (B.G. Hill).

https://doi.org/10.1016/j.redox.2018.05.016
Received 14 May 2018; Received in revised form 24 May 2018; Accepted 30 May 2018
Available online 01 June 2018

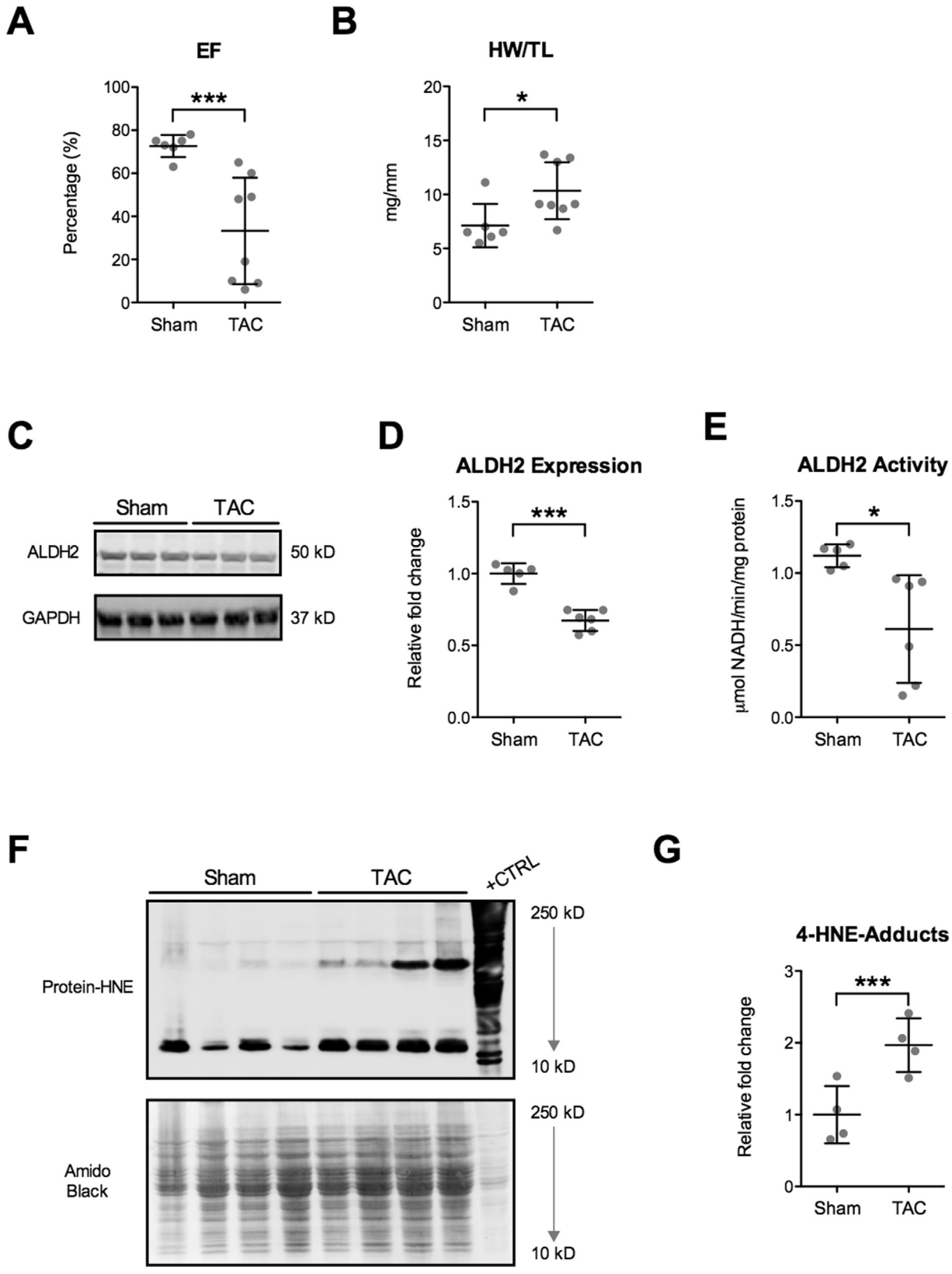

Fig. 1. Pressure overload-induced heart failure is associated with decreases in cardiac ALDH2 activity. Cardiac function and ALDH2 expression and activity in wild-type mice subjected to sham surgery or transverse aortic constriction (TAC) for 12 weeks: Shown are (**A**) ejection fraction measured by echocardiography. Additional echocardiographic parameters can be found in Table 1; (**B**) Gravimetric measurements of heart mass in Sham and TAC mice; (**C**) Representative Western blot of ALDH2; (**D**) Densitometric measurements from panel C; (**E**) ALDH2 activity measurements. n = 5–8 per group; *p ≤ 0.05, ***p < 0.001, ****p ≤ 0.0001; in panel E, Welch's correction was applied because equal variances cannot be assumed; (**F**) Representative Western blot of protein-4-hydroxynonenal (HNE) adducts from sham and TAC hearts. Heart homogenates incubated with reagent HNE served as a positive control; and (**G**) Densitometric measurements from panel F. n = 4 per group, *p < 0.05.