FEATURES

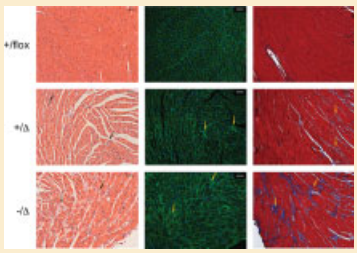
VOLUME 116 • NUMBER 11

Journal of Cellular Biochemistry

Cardiac-Specific Disruption of Bin1 in Mice Enables a Model of Stress- and Age-Associated Dilated Cardiomyopathy

Lisa D. Laury-Kleintop, Jennifer R. Mulgrew, Ido Heletz, Radu Alexandru Nedelcoviciu, Mee Young Chang, David M. Harris, Walter J. Koch, Michael D. Schneider, Alexander J. Muller, and George C. Prendergast

ACCEPTED MANUSCRIPT ONLINE 2 MAY 2015



Non-compensated dilated cardiomyopathy (DCM) leading to death from heart failure is rising rapidly in developed countries due to aging demographics, and there is a need for informative preclinical models to guide the development of effective therapeutic strategies to prevent or delay disease onset. In this study, we describe a novel model of heart failure based on cardiac-specific deletion of the prototypical mammalian BAR adapter-encoding gene *Bin1*, a modifier of age-associated disease. *Bin1* deletion during embryonic development causes hypertrophic cardiomyopathy and neonatal lethality, but there is little information on how *Bin1* affects cardiac function in adult animals. Here we report that cardiomyocyte-specific loss of *Bin1* causes age-associated dilated cardiomyopathy (DCM) beginning by 8–10 months of age. Echocardiographic analysis showed that *Bin1* loss caused a 45% reduction in ejection fraction during aging. Younger animals rapidly developed DCM if cardiac pressure overload was created by transverse aortic constriction. Heterozygotes exhibited an intermediate phenotype indicating *Bin1* is haplo-insufficient to sustain normal heart function. *Bin1* loss increased left ventricle (LV) volume and diameter during aging, but it did not alter LV volume or diameter in hearts from heterozygous mice nor did it affect LV mass. *Bin1* loss increased interstitial fibrosis and mislocalization of the voltage-dependent calcium channel $Ca_v1.2$, and the lipid raft scaffold protein caveolin-3, which normally complexes with Bin1 and $Ca_v1.2$ in cardiomyocyte membranes. Our findings show how cardiac deficiency in Bin1 function causes age- and stress-associated heart failure, and they establish a new preclinical model of this terminal cardiac disease.

Histone Deacetylase Inhibition Impairs Normal Intestinal Cell Proliferation and Promotes Specific Gene Expression

Alireza Roostaee, Amel Guezguez, Marco Beauséjour, Aline Simoneau, Pierre H. Vachon, Emile Levy, and Jean-François Beaulieu

ACCEPTED MANUSCRIPT ONLINE 30 JUNE 2015

Mechanisms that maintain proliferation and delay cell differentiation in the intestinal crypt are not yet fully understood. We have previously shown the implication of histone methylation in the regulation of enterocytic differentiation. In this study, we investigated the role of histone deacetylation as an important epigenetic mechanism that controls proliferation and differentiation of intestinal cells using the histone deacetylase inhibitor suberanilohydroxamic acid (SAHA) on the proliferation and differentiation of human and mouse intestinal cells. Treatment of newly confluent Caco-2/15 cells with SAHA resulted in growth arrest, increased histone acetylation and up-regulation of the expression of intestine-specific genes such as those encoding sucrase-isomaltase, villin and the ion exchanger SLC26A3. Although SAHA has been recently used in clinical trials for cancer treatment, its effect on normal intestinal cells has not been documented. Analyses of small and large intestines of mice treated with SAHA revealed a repression of crypt cell proliferation and a higher expression of sucrase-isomaltase in both segments compared to control mice. Expression of SLC26A3 was also significantly up-regulated in the colons of mice after SAHA administration. Finally, SAHA was also found to strongly inhibit normal human intestinal crypt cell proliferation in vitro. These results demonstrate the important implication of epigenetic mechanisms such as histone acetylation/deacetylation in the regulation of normal intestinal cell fate and proliferation.