P1025

Promotion of Adult Heart Regeneration by Dual Function of Histone Deacetylase 7

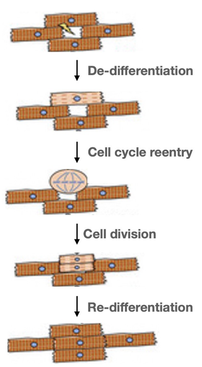
Jihyun Jang and Deqiang Li

Department of Surgery, The Center For Vascular & Inflammatory Disease,
University of Maryland School of Medicine, Baltimore, MD, USA

BACKGROUND

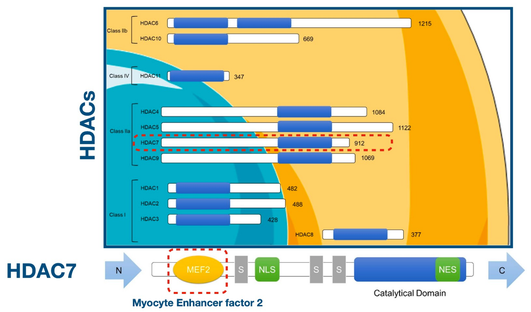
Mammalian adult heart regeneration

- Adult heart is poorly regenerative.
- However, cell cycle activation is not necessarily converted to a true cell division, but rather as multi-nucleation or polyploidy.
- Alternatively, adult heart might accomplish regeneration by dual function, cardiomyocyte dedifferentiation and proliferation



Histone Deacetylase 7 (HDAC7)

- HDAC7 belongs to class II HDACs.
- Unlike Class I HDACs, which are ubiquitously expressed, Class II HDACs have restricted tissue and organ expression pattern.
- HDAC7 has been shown to be crucial to maintaining vascular integrity during heart development, and it regulates myoblast differentiation by interacting with myocyte enhancer factor-2 (MEF2).

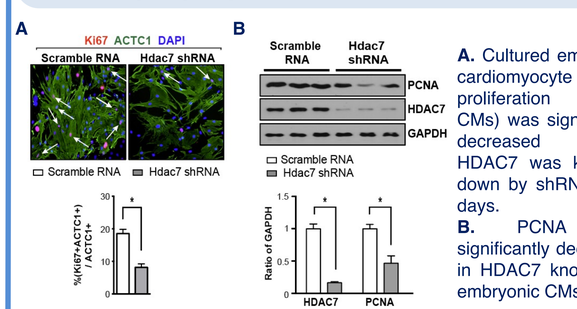


Asfaha et al. *Bioorg Med Chem* (2019)

Financial Disclosure - *None*

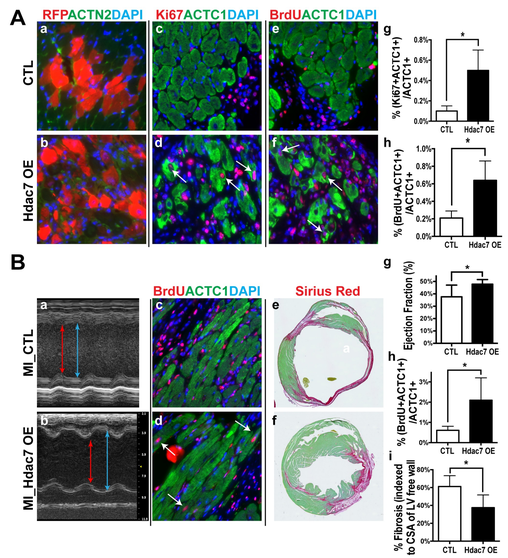
RESULTS

Fig 1. Knockdown of HDAC7 decreases cardiomyocyte proliferation.



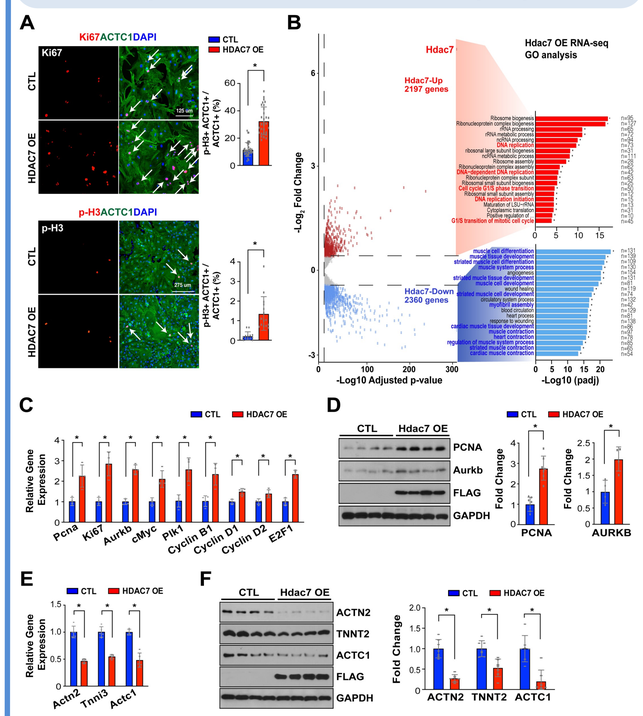
A. Cultured embryonic cardiomyocyte (CM) proliferation (Ki67+ CMs) was significantly decreased when HDAC7 was knocked down by shRNA for 3 days.
B. PCNA was significantly decreased in HDAC7 knockdown embryonic CMs.

Fig 2. Overexpression of HDAC7 increased the cardiomyocyte proliferation and rescued the heart function from myocardial infarction.



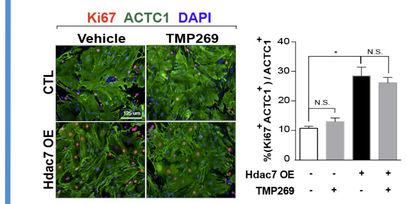
A. Significant increase of Ki67+ and BrdU+ CMs in HDAC7 overexpression (OE) hearts. Arrows point to Ki67+ or BrdU+ CMs. **B.** (a, b, g) Significant improvement of ejection fraction in the myocardial infarction (MI) hearts injected with Hdac7 adenovirus as compared to the MI hearts injected with mCherry adenovirus (MI_CTL); (c, d, h) Significant increase of CM proliferation (BrdU+ CMs) in the Hdac7 OE MI; (e, f, i) Significant reduction of scar size in the Hdac7 OE MI.

Fig 3. HDAC7 OE induced cell dedifferentiation and cell cycle activation in cardiomyocytes



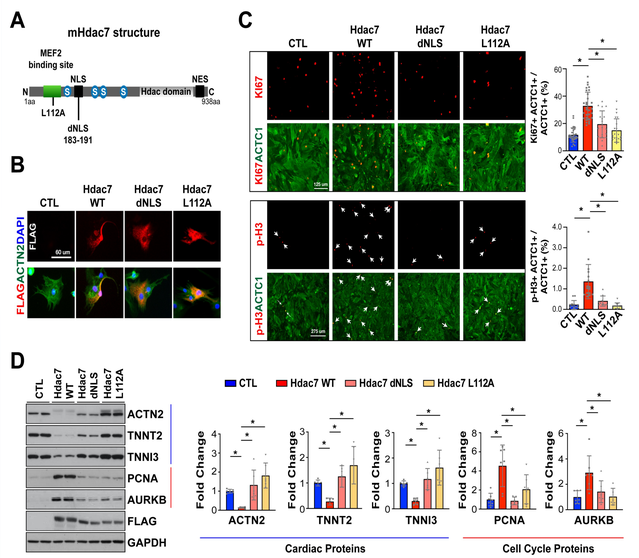
A. BrdU+ and p-H3+ CMs are increased in Hdac7 OE. **B.** Gene Ontology-analysis showed that Hdac7 down regulates cardiac sarcomeric genes, while up regulates cell cycle genes. **C and D.** Proliferation markers are significantly increased in Hdac7 OE. **E and F.** Sarcomere markers are decreased in Hdac7 OE.

Fig 4. Deacetylase activity of HDAC7 is not required for effect of HDAC7 on cardiomyocyte proliferation



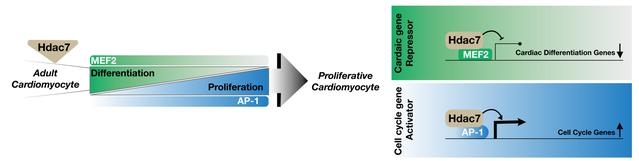
TMP269 (working conc: 36 nM), HDAC7 deacetylase inhibitor, does not affect HDAC7 induced CM proliferation

Fig 5. MEF2 binding site of HDAC7 is required for dedifferentiation and proliferation in cardiomyocytes.



A. Schematic of mouse HDAC7 protein. **B.** Expression pattern of Hdac7 in NMCMs. **C.** Loss of Mef2 binding site abolished proliferation effect by Hdac7 in NMCMs. **D.** The expression of cardiac (a-actinin, cTnT and cTn I) and cell cycle proteins (PCNA and Aurkb) 3 days after infection of mCherry, Hdac7 WT, Hdac7 dNLS and L112A adenoviruses in Neonatal CMs.

CONCLUSION



- **Hdac7 promotes cardiomyocyte proliferation *in vitro* and *in vivo*.**
- **Hdac7 inhibits expression of cardiac genes by interacting with MEF2 and activates cell cycle in cardiomyocytes**

❖ **This research was supported by by the National Heart, Lung, and Blood Institute R01 grant HL153406 (D.L.)**