Ctnna3 Deficiency Promotes Heart Regeneration by Enhancing Cardiomyocyte Proliferation in Neonatal Mice

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Abstract

Heart regeneration requires renewal of lost cardiomyocytes. However, the mammalian heart loses its proliferative capacity soon after birth, and the molecular signaling underlying the loss of cardiac proliferation postnatally is not fully understood. Here we report that ablation of Ctnna3, coding for an αT-catenin protein and highly expressed in hearts, accelerated heart regeneration following heart apex resection in neonatal mice. Our results show that Ctnna3 deficiency enhances cardiomyocyte proliferation in hearts from P7 mice by upregulating Yap expression. Our study demonstrates that Ctnna3 deficiency is sufficient to promote heart regeneration and cardiomyocyte proliferation in neonatal mice and indicates that functional interference of α-catenins might help to stimulate myocardial regeneration after injury.

Introduction

Heart failure resulting from the loss of cardiomyocytes during injury and disease is a primary cause of human morbidity and mortality [1]. The adult mammalian heart only has limited cardiomyocyte turnover, and this is not sufficient to restore contractile function after heart injury. In contrast, the neonatal mammalian heart possesses a remarkable capacity for cardiac regeneration, but this heart regeneration ability after injury is lost by 7 days of age, a time point that coincides with the onset of cardiomyocyte proliferative arrest [2–4]. Multiple experimental strategies have been explored to restore functional myocardium for repairing the injured heart. These are: (a) cell therapy using embryonic stem cells, induced pluripotent stem cells (iPS) and cardiac progenitor cells; (b) reprogramming of nonmyocytes, e.g. cardiac fibroblasts, to a cardiac cell fate (cardiomyocytes) using cardiogenic genes and small molecules; (c) re-activation of cardiomyocyte mitosis in the adult heart [5–8]. Genetic fate-mapping experiments in the neonatal mice [3] and adult zebrafish [9, 10] indicate that the regenerated cardiomyocytes are mainly derived from reactivation of preexisting cardiomyocytes, rather than activation of undifferentiated stem or progenitor cells. Thus, the identification of genes and a thorough understanding of the mechanisms underlying the regulation of cardiomyocyte proliferation and regeneration may provide critical information for design of new therapeutic strategies to heart failure.

Alpha-catenins (α-catenins) play fundamental roles in cadherin-mediated cell-cell adhesion and actin dynamics [11–13]. They function widely in regulating cell differentiation, proliferation, and regeneration [12–14]. There are three subtypes of α-catenins: namely αE-catenin, αN-catenin, and αT-catenin, encoded by Ctnna1, Ctnna2, and Ctnna3 respectively, in mammals [15, 12, 14]. They share substantial similarity of amino-acid sequences but have distinct tissue distribution. αE-catenin is a well-known tumor suppressor with broad expression profile[12]. αN-catenin is restricted to neuronal tissues [16] and αT-catenin is the newest identified member of α-catenin family and primarily expressed in heart tissue and testis [15]. Although cardiac-specific deletion of Ctnna1 resulted in progressive dilated cardiomyopathy and susceptibility to wall rupture in adult mice [17] and Ctnna3 deficient mice displayed ventricular arrhythmia and dilated cardiomyopathy after acute ischemia [18], enhanced cardiomyocyte proliferation was observed in hearts from cardiac-specific Ctnna1 and Ctnna3 double knockout mice[19]. In addition,
mutations in human $CTNNA3$ were identified in patients with arrhythmogenic right ventricular cardiomyopathy [20]. However, whether αE-catenin or αT-catenin deficiency alone promotes heart regeneration and cardiomyocyte proliferation remains elusive.

Here we present the experimental evidence that $Ctnna3$ deficiency solely is sufficient to promote heart regeneration following heart apex resection in neonatal mice. Our study revealed that cardiomyocyte proliferation was increased in neonatal $Ctnna3$ deficient mice, probably by up-regulating $Yap$ expression. These results suggest that αT-catenin does contribute to regulation of heart regeneration and cardiomyocyte proliferation in neonatal mice.

**Materials And Methods**

**Animals**

The $Ctnna3^{−/−}$ mice (a kind gift from Dr. Radice’s lab at Thomas Jefferson University, Philadelphia, PA, USA) have been characterized previously [18]. $Ctnna3^{−/−}$ (C57/129) mice were crossed to wildtype (WT) FVB mice to generate $Ctnna3^{+/−}$ mice. These mice were maintained and raised on a C57/129/FVB genetic background in a specific pathogen-free facility. Experiments were performed in accordance with “the National Institutes of Health guide for the care and use of laboratory animals” and approved by Use Committee of the Institute of Developmental Biology and Molecular Medicine at Fudan University, Shanghai, China.

**Isolation And Culture Of Neonatal Mouse Cardiomyocytes**

Cardiomyocytes from neonatal mice were isolated as previously described [19]. Briefly, hearts from neonatal mice at postnatal day 1 (P1) were disassociated with collagenase II. The disassociated cells were plated in a 10cm plate for 2 hours with DMEM/F12 medium, and the supernatant was collected and cells were re-plated on laminin-coated glass coverslips in 12-well plates at $3 \times 10^5$ cells per well. On the following day, the proliferating cells were labeled by EdU in fresh medium for 24 hours and detected using Cell-light EdU Apollo 643 In Vitro Kit (#C10310–2, RiboBio, Guangzhou, China) following the manufacturers’ instructions.

**Neonatal Mouse Apical Resection**

Neonatal mouse apical resection of hearts from P1 pups was performed as described previously [21].

**Histological And Immunofluorescent Analyses**
Tissue processing, frozen sections and immunofluorescent microscopic analysis were performed as previously described [22]. Briefly, for frozen sections, mouse hearts were dissected out, fixed with 4% PFA in PBS overnight, dehydrated with 30% sucrose at 4°C for 3 days and then embedded in OCT (Richard-Allan Scientific). Sections were collected at 10µm.

For histological analysis, mouse hearts were paraffinized and were sectioned at 4 µm followed by hematoxylin/eosin (H&E) staining or Masson's trichrome (MT) staining (G1340, Solarbio, Beijing, China) as previously described[23]. For quantification of cardiac fibrosis, images of the MT stained sections were captured with Leica Aperio VERSA microscope (Leica Biosystems, Germany) and the area of fibrosis in heart apex was determined using Visiopharm software (Visiopharm, Horsholm, Denmark).

For in vivo EdU (5-ethynyl-2′-deoxyuridine) assay, WT or Ctnna3−/− mice at P2 were injected intraperitoneally with 50mg/kg EdU. Twenty four hours after injection, the mouse hearts were dissected out and processed for frozen section. EdU assay was performed using the Kit (#C10310–2, RiboBio, Guangzhou, China) following the manufacturers’ instructions.

For immunofluorescent analysis, the sections were stained with antibodies against the following proteins: sarcomeric α-Actinin (#A7732, Sigma, USA); Phospho-his tone H3(PH3) (#53348) and PCNA(#2586) from Cell Signaling Technology, USA. Fluorescence micrographs were acquired using a Zeiss LSM710 confocal microscope.

**Western Blotting**

Standard Western blot protocol was followed. Protein extracts were prepared with RIPA buffer and then subjected to SDS-PAGE. The antibodies against the following proteins were used in our study: αT-catenin (#13974-1-AP, Proteintech, USA), β-catenin(#51067-2-AP, Proteintech, USA), and Yap (14074T, Cell Signaling, USA). The protein bands were detected with an ECL Western Blotting Analysis System. The images were obtained by Tanon-5200, and the density of bands was determined with Image J.

**Statistical analysis**

Unpaired Student's t-test by GraphPad Prism was conducted for statistical analysis.

**Results**

Loss of Ctnna3 accelerates heart regeneration in neonatal mice after heart apex resection.

Although the mammalian adult heart is generally considered nonregenerative, neonatal mouse hearts have a genuine capacity to regenerate following apex resection [1, 3]. To evaluate whether Ctnna3 affects heart regeneration, we performed surgical apical resection of hearts (5%~10% of the ventricular myocardium) of WT and Ctnna3−/− neonatal mice at P1 and harvested hearts at 7 and 14 day(s) post-
resection (dpr) (Fig. 1A) for histological analysis and immunofluorescence staining with antibody against PCNA, separately. The results revealed that, as reported by Porrello [24], the resection plane was characterized by progressive regeneration of the apex with some restoration of the resected myocardium within 14 days (Fig. 1B). The Masson's trichrome staining showed that the accumulation of fibrotic tissue (blue staining in Fig. 1C) in hearts from Ctnna3−/− mice at 14dpr dramatically decreased compared with WT mice (Fig. 1C and D). The number of PCNA-positive cells in the border zone of regenerated hearts of Ctnna3−/− neonatal mice at 7 dpr was significantly higher than the counterpart in hearts of WT neonatal mice (Fig. 1E and F). As heart regeneration is thought to occur primarily through cardiomyocyte proliferation [25, 10], our results suggest that loss of Ctnna3 may enhance heart regeneration by promoting cardiomyocyte proliferation in neonatal mice.

Ctnna3 deficiency promotes cell proliferation in neonatal mouse hearts

Since cardiomyocytes in neonatal mouse heart retain active proliferation before postnatal day 7 [26], we tested whether Ctnna3 deficiency promoted cardiomyocyte proliferation in neonatal mice. The ventricles of WT and Ctnna3−/− mice at P1, P3, P7 were sectioned and stained separately with antibodies against phospho-histone H3 (PH3) (a marker of mitosis)[27], and Sarcomeric α-actinin (a specific marker for α-skeletal and α-cardiac muscle actinins) [28]. Quantification of PH3-positive cardiomyocytes revealed that cardiomyocyte proliferation was strikingly increased in the ventricles of Ctnna3−/− neonatal mice at P3 and P7 (Fig. 2A, B), but not at P14 compared to WT counterparts.

To further verify the enhanced cell proliferation in Ctnna3−/− neonatal mice, the proliferating cells in Ctnna3−/− and WT neonatal mice at P7 were in vivo EdU-pulse labeled and detected by EdU staining (see Materials and Methods). The results showed that the number of EdU-positive cells was significantly increased in ventricles and atriums of Ctnna3−/− neonatal mice compared to those in control littermates (Fig. 2C-F). These results demonstrate that Ctnna3 deficiency promotes cell proliferation in neonatal mouse hearts.

Ctnna3 deficiency promotes proliferation of primary cardiomyocytes

Since heart is mainly composed of cardiomyocytes, in addition to several other types of cells, such as cardiac fibroblasts, endothelial cells, and smooth muscle cells [29], we hypothesized that Ctnna3 deficiency promoted the proliferation of cardiomyocytes. To test this hypothesis, primary cardiomyocytes were isolated from P5 WT and Ctnna3−/− mouse hearts and pulse-labelled with EdU in vitro followed by immunostaining with antibody against sarcomeric α-actinin and EdU staining. Our study revealed that a significant increase of the proportion of the EdU-positive cardiomyocytes (proliferating cardiomyocytes) from Ctnna3−/− neonatal mice compared to that from WT mice at P5 (Fig. 3A and B). These results demonstrate that the loss of Ctnna3 promotes proliferation of cardiomyocytes in neonatal mice.

Loss of Ctnna3 enhances Yap expression
Alpha-catenins directly bind to both β-catenin and actin filaments, thereby coupling stable actin filaments to the cadherin adhesion molecules [11, 16, 13]. β-catenin is also a well-documented positive regulator for cell proliferation. To study the mechanism(s) by which αT-catenin deficiency promotes cell proliferation, the expression level of β-catenin in hearts from Ctnna3−/− and WT mice at P7 was evaluated by Western blotting. The result showed that the protein level of β-catenin was not significantly changed between WT and Ctnna3−/− hearts (Fig. 3C and D).

The Hippo pathway is a key regulatory signaling pathway for heart development and organ size [30]. Thus, we inspected whether loss of Ctnna3 only had any effect on Yap expression in the neonatal heart. Our study revealed that the protein level of Yap significantly increased in hearts from P7 Ctnna3−/− mice compared to that in control mouse hearts (Fig. 3C and D). This result suggests that Ctnna3 deficiency may promote neonatal cardiomyocyte proliferation by enhancing Yap expression.

**Discussion**

Previous study showed that cardiac-specific Ctnna1 (αE-catenin) deficient adult mice displayed progressive dilated cardiomyopathy[17] and Ctnna3 (αT-catenin) deficient adult mice exhibited dilated cardiomyopathy only after acute ischemia[18], but without affecting the number of cardiomyocytes. Li, et al., also demonstrated that simultaneously cardiac-specific deleting Ctnna1 and Ctnna3 in mice at perinatal stage resulted in an increased cardiomyocyte number and cardiomyocyte proliferation in the postnatal heart [19]. Although these results strongly suggest that Ctnna1 and Ctnna3 jointly play an important but redundant role in the inhibition of cardiomyocyte proliferation, whether Ctnna3 contributes to heart regeneration or Ctnna3 is adequate to suppress cardiomyocyte proliferation at neonatal stage needs to be addressed. Here we present in vivo evidences that Ctnna3 deficient only is sufficient to enhance heart regeneration and cardiomyocyte proliferation in neonatal mice. Hence, functional interference of α-catenins may provide a potential strategy to promote myocardial regeneration after injury.

**Declarations**

**Declaration of competing interest**

The authors declare that they have no conflicts of interest with the contents of this article.

**Authors’ contribution: Zou and Dai work at data analysis.**

Sha Zou and Wuhou Dai were responsible for the data acquisition, data analysis and writing. Jifen Li and Hongyan Wang provided the Ctnna3−/- mice, Yuan Lin, Juan Liu and Wufan Tao provided ideas of research, paper modification and critical reading of the manuscript. All authors have approved the final manuscript.

**Ethics approval:**
Experiments were performed in accordance with “the National Institutes of Health guide for the care and use of laboratory animals” and approved by Use Committee of the Institute of Developmental Biology and Molecular Medicine at Fudan University, Shanghai, China.

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References

1. Laamme MA, Murry CE (2011) Heart regeneration. Nature 473:326–335. doi:10.1038/nature10147
2. Li F, Capasso WX, Gerdes JM AM (1996) Rapid transition of cardiac myocytes from hyperplasia to hypertrophy during postnatal development. J Mol Cell Cardiol 28:1737–1746
3. Porrello ER, Mahmoud AI, Simpson E, Hill JA, Richardson JA, Olson EN, Sadek HA (2011) Transient regenerative potential of the neonatal mouse heart. Science 331:1078–1080. doi:10.1126/science.1200708
4. Walsh S, Ponten A, Fleischmann BK, Jovinge S (2010) Cardiomyocyte cell cycle control and growth estimation in vivo-an analysis based on cardiomyocyte nuclei. Cardiovasc Res 86:365–373. doi:10.1093/cvr/cvq005
5. De Leon JR, Federoff HJ, Dickson DW, Vikstrom KL, Fishman GI (1994) Cardiac and skeletal myopathy in beta myosin heavy-chain simian virus 40 tsA58 transgenic mice. Proc Natl Acad Sci U S A 91:519–523. doi:10.1073/pnas.91.2.519
6. Klug MG, Soonpaa MH, Koh GY, Field LJ (1996) Genetically selected cardiomyocytes from differentiating embryonic stem cells form stable intracardiac grafts. J Clin Invest 98:216–224. doi:10.1172/jci118769
7. Ma H, Yin C, Zhang Y, Qian L, Liu J (2016) ErbB2 is required for cardiomyocyte proliferation in murine neonatal hearts. Gene 592:325–330. doi:10.1016/j.gene.2016.07.006
8. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM et al. (2001) Bone marrow cells regenerate infarcted myocardium. Nature 410:701–705. doi:10.1038/35070587
9. Jopling C, Sleep E, Raya M, Marti M, Raya A, Izpisua Belmonte JC (2010) Zebrafish heart regeneration occurs by cardiomyocyte dedifferentiation and proliferation. Nature 464:606–609. doi:10.1038/nature08899
10. Kikuchi K, Holdway JE, Werdich AA, Anderson RM, Poss KD (2010) Primary contribution to zebrafish heart regeneration by Gata4 cardiomyocytes. Nature 464:601–605
11. Drees F, Pokutta S, Yamada S, Nelson WJ, Weis WI (2005) Alpha-catenin is a molecular switch that binds E-cadherin-beta-catenin and regulates actin-filament assembly. Cell 123:903–915.
12. Kobielak A, Fuchs E (2004) Alpha-catenin: at the junction of intercellular adhesion and actin dynamics. Nat Rev Mol Cell Biol 5:614–625. doi:10.1038/nrm1433

13. Scott JA, Yap AS (2006) Cinderella no longer: alpha-catenin steps out of cadherin's shadow. J Cell Sci 119:4599–4605. doi:10.1242/jcs.03267

14. Vite A, Li J, Radice GL (2015) New functions for alpha-catenins in health and disease: from cancer to heart regeneration. Cell Tissue Res 360:773–783. doi:10.1007/s00441-015-2123-x

15. Janssens B, Goossens S, Staes K, Gilbert B, van Hengel J, Colpaert C, Bruyneel E, Mareel M, van Roy F (2001) αT-Catenin: a novel tissue-specific β-catenin-binding protein mediating strong cell-cell adhesion. J Cell Sci 114:3177–3188

16. Hirano S, Kimoto N, Shimoyama Y, Hirohashi S, Takeichi M (1992) Identification of a neural α-catenin as a key regulator of cadherin function and multicellular organization. Cell 70:293–301. doi:http://dx.doi.org/10.1016/0092-8674(92)90103-J

17. Sheikh F, Chen Y, Liang X, Hirschy A, Stenbit AE, Gu Y, Dalton ND, Yajima T, Lu Y, Knowlton KU et al. (2006) alpha-E-catenin inactivation disrupts the cardiomyocyte adherens junction, resulting in cardiomyopathy and susceptibility to wall rupture. Circulation 114: 1046–1055, doi:10.1161/CIRCULATIONAHA.106.634469

18. Li J, Goossens S, van Hengel J, Gao E, Cheng L, Tyberghein K, Shang X, De Rycke R, van Roy F, Radice GL (2012) Loss of alphaT-catenin alters the hybrid adhering junctions in the heart and leads to dilated cardiomyopathy and ventricular arrhythmia following acute ischemia. J Cell Sci 125:1058–1067. doi:10.1242/jcs.098640

19. Li J, Gao E, Vite A, Yi R, Gomez L, Goossens S, van Roy F, Radice GL (2015) Alpha-catenins control cardiomyocyte proliferation by regulating Yap activity. Circ Res 116:70–79. doi:10.1161/CIRCRESAHA.116.304472

20. Van Hengel J, Calore M, Bauce B, Dazzo E, Mazzotti E, De Bortoli M, Lorenzon A, Mura IEAL, Beffagna G, Rigato I (2013) Mutations in the area composita protein αT-catenin are associated with arrhythmogenic right ventricular cardiomyopathy. Eur Heart J 34:201–210

21. Mahmoud AI, Porrello ER, Kimura W, Olson EN, Sadek HA (2014) Surgical models for cardiac regeneration in neonatal mice. Nat Protoc 9:305–311. doi:10.1038/nprot.2014.021

22. Peng C, Ye J, Yan S, Kong S, Shen Y, Li C, Li Q, Zheng Y, Deng K, Xu T et al. (2012) Ablation of vacuole protein sorting 18 (Vps18) gene leads to neurodegeneration and impaired neuronal migration by disrupting multiple vesicle transport pathways to lysosomes. The Journal of biological chemistry 287: 32861–32873, doi:10.1074/jbc.M112.384305

23. Schulz C, Chen J, Lee SK, Abd-Elgaliel WR, Liang L, Galende E-Y, Hajjar RJ, Tung C-H (2011) Assessment of Cardiovascular Fibrosis Using Novel Fluorescent Probes. PLoS ONE 6:e19097. doi:10.1371/journal.pone.0019097

24. Porrello ER, Simpson MA, Johnson E, Grinsfelder BA, Canseco D, Mammen D, Rothermel PP, Olson BA, Sadek EN HA. Proc.. (2013) Regulation of neonatal and adult mammalian heart regeneration by
the miR-15 family. *Natl. Acad. Sci. U. S. A.* 110: 187–192

25. Jopling C, Sleep E, Raya M, Marti M, Raya A, Belmonte, J.C.I. Zebrafish heart regeneration occurs by cardiomyocyte dedifferentiation and proliferation. *Nature* 464: 606–609

26. Walsh S, Pontén A, Fleischmann BK, Jovinge S Cardiomyocyte cell cycle control and growth estimation in vivo—an analysis based on cardiomyocyte nuclei. *Cardiovascular Research* 86: p.365–373

27. Kang TH, Park DY, Choi YH, Kim KJ, Yoon HS, Kim KT (2007) Mitotic histone H3 phosphorylation by vaccinia-related kinase 1 in mammalian cells. Mol Cell Biol 27:8533–8546. doi:10.1128/MCB.00018-07

28. Sorimachi H, Kolmerer BIS, Stier G, Gregorio CLD, Linke WA, Suzuki K, Labeit S, Freiburg A (1997) Tissue-specific expression and α-actinin binding properties of the Z-disc titin: implications for the nature of vertebrate Z-discs. J Mol Biol 270:688–695

29. Banerjee I, Fuseler JW, Price RL, Borg TK, Baudino TA (2007) Determination of cell types and numbers during cardiac development in the neonatal and adult rat and mouse. Am J Physiol Heart Circ Physiol 293:H1883–H1891

30. Zhou Q, Li L, Zhao B, Guan K-L (2015) The Hippo Pathway in Heart Development, Regeneration, and Diseases. Circ Res 116:1431–1447. doi:10.1161/circresaha.116.303311

**Figures**
Figure 1

Ctnna3 deficiency promotes heart regeneration in neonatal mice after heart apical resection. A. The scheme of the open thoracotomy experiment. P1: postnatal day 1; dpr: day(s) post-resection. B-C. Representative images of paraffin heart sections from WT and Ctnna3-/- mice at 14 dpr stained with HE (B) or Masson’s trichrome (C). Low panels in (C) are enlarged views of the cropped regions in up panels in (C). Bars=50μm. D-E. Statistics analysis of the area of fibrotic tissue per field in C (WT, n =3; Ctnna3-/-,
n=3) and PCNA-positive cells per field at apex in (F) (WT, n =5; Ctnna3-/-, n=5). F. Representative fluorescent images of frozen sections of mouse hearts at 7 dpr stained with anti-PCNA. White dash lines mark the resection boundaries. Bars=50μm. Values in D and E represent the means ± SD. *, p<0.05.

Figure 2

Enhanced cell proliferation in hearts of Ctnna3-/- neonatal mice. A. Representative florescent images of mouse heart sections from P7 WT and Ctnna3-/- mice co-stained with anti-PH3 (for prophase mitotic
cells) and anti-Sarcomeric-α-actinin (for Cardiomyocytes). Bar=200μm. B. Statistics analysis of PH3-positive cells per field (WT, n=5; Ctnna3-/-, n=5). C and E. Representative fluorescent images of the sections of atrium (C) and ventricle (E) from P7 WT and Ctnna3-/- neonatal mice pulse-labelled with EdU. Bars=50μm. D and F. Statistics analysis of EdU-positive cells per field (WT, n=5; Ctnna3-/-, n=5) in C and E. Values in B, D and F represent the means ± SD. **, p<0.01, *, p<0.05 ns, not significant.

Figure 3

Ctnna3 deficiency promotes proliferation of primary cardiomyocytes and up regulates YAP expression. A. Representative fluorescent images of cultured primary mouse cardiomyocytes from neonatal WT and Ctnna3-/- mice. The cultured cells were pulse-labeled with EdU for 24 hrs followed by fluorescent staining. Bar=100μm. B. Statistics analysis of EdU-positive cardiomyocytes per field in A. (WT, n=9; Ctnna3-/-, n=12). C-D, Western blot analysis (C) and quantification (D) of α-catenin and Yap protein expression in...
hearts from WT and Ctnna3 deficient mice. (n=3 for WT and Ctnna3/-, respectively). Values in B and D represent the means ± SD. *, p<0.05.