Releasing YAP From an α-Catenin Trap Increases Cardiomyocyte Proliferation

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Adult mammalian cardiomyocytes possess little endogenous proliferative capacity. This innate limitation underlies our inability to reverse heart failure and improve patient outcome after myocardial injury. The mechanisms that restrict adult mammalian cardiomyocyte proliferation have been the intensely scrutinized, and molecular insights are slowly emerging.1 In this issue of Circulation Research, Li et al2 add an important new insight by showing that α-catenins, components of cardiomyocyte intercellular junctions, restrain the mitogenic transcriptional coactivator Yes-associated protein (YAP) and thereby inhibit cardiomyocyte proliferation.

The essential function of cardiac adherens junctions to join cardiomyocytes mechanically was vividly exposed by genetic inactivation of several intercalated disk components, including γ-, δE-, and αT-catenins. Loss of γ-catenin caused fetal demise from heart defects and ventricular rupture.2 Fetal cardiomyocyte-restricted αE-catenin inactivation was compatible with embryonic survival, but mice had cardiomyocyte apoptosis and ventricular dilatation and thinning.3 These mice were also predisposed to ventricular rupture after myocardial infarction (MI). Mice lacking αT-catenin similarly survived to term, developed progressive cardiomyopathy, and were more susceptible to ischemia-induced arrhythmias, associated with mislocalization of gap junctions and loss of plakophilin-2 from area composita.4

In addition to their essential roles in maintaining the mechanical integrity of the heart, adherens junctions are ideally positioned as signaling centers that transduce mechanical forces. The signaling functions of adherens junctions are best highlighted by their role in the pathogenesis of arrhythmogenic cardiomyopathy, in which desmosome gene mutations cause fibrofatty infiltration of the ventricular wall and a high risk of ventricular arrhythmia. Arrhythmogenic cardiomyopathy mutations destabilize desmosomes and diminish γ-catenin localization to intercalated disks. The liberated γ-catenin has been proposed to compete with its closely related cousin, β-catenin, and thereby dampen Wnt/β-catenin signaling.5 This altered canonical Wnt signaling may contribute to the adipogenic changes characteristic of arrhythmogenic cardiomyopathy. More recently, desmosome mutations in arrhythmogenic cardiomyopathy were linked to modulation of Hippo/YAP signaling, an important pathway that regulates organ size and cellular proliferation and survival6 and that also modulates canonical Wnt signaling.7 Desmosome mutations increased activation of NF2, an upstream regulator of the Hippo kinase cascade. As a result, Hippo kinase phosphorylation of the YAP transcriptional coactivator increased, resulting in YAP sequestration near the membrane and reduced transcriptional activity.8

The study of Li et al2 defines a new inter-relationship between intercalated disks and YAP activity. They studied mice with fetal, cardiomyocyte-specific inactivation of both αE- and
αT-catenin driven by Myh6-Cre. These double knockout (DKO) mice survived to postnatal life. At 6 weeks, the hearts were normal in size, but cardiomyocyte number was higher and cardiomyocyte size was lower than controls. Increased cardiomyocyte number was linked to greater cell cycle activity. Previously, αE-catenin was shown to mediate contact inhibition of keratinocyte proliferation via sequestration of YAP at adherens junctions. Therefore, Li et al. investigated YAP activity in the αE/αT DKO hearts and found increased nuclear YAP. Enhanced YAP activity was essential for the proliferative effect of α-catenin loss of function because increased cell cycle activity observed in cultured neonatal cardiomyocytes with siRNA-mediated αE/αT knockdown was blunted by simultaneous YAP knockdown. Interestingly, the mechanism of YAP activation seems to differ from what was previously reported for αE-catenin regulation of YAP in keratinocytes, where αE-catenin inhibited YAP dephosphorylation by the phosphatase PP2Ac. In contrast, in DKO hearts, both phospho- and total YAP levels were increased, leading to more activated YAP but only a slight reduction of the phospho:total YAP ratio. Additional studies are needed to define the mechanistic link between αE/αT-catenin ablation in DKO hearts and YAP activation.

Li et al. also examined the effect of αE/αT-catenin ablation in adult cardiomyocytes driven by Myh6-MerCreMer. Although fetal inactivation of either αE- or αT-catenin caused adult onset cardiomyopathy, interestingly, adult stage inactivation of both αE/αT-catenin (IN-DKO) was compatible with survival for >1 year and did not cause histological abnormalities. Cardiomyocyte proliferation was not elevated in unstressed hearts. However, MI of IN-DKO mice showed that the inactivation of αE/αT-catenins had a surprising protective effect: IN-DKO mice had better cardiac function and reduced cardiac remodeling at 9 and 12 weeks post MI. These changes were associated with increased cardiomyocyte cell cycle activity in the border and ischemic zones, and with an increased fraction of cardiomyocytes with YAP nuclear localization. These data suggested that YAP activity in unstressed adult cardiomyocytes is restrained by multiple mechanisms in addition to binding to α-catenins. Myocardial injury releases these additional restraints and unmasks a rate-limiting role for α-catenin trapping of YAP at area composita to limit cardiomyocyte proliferation. Thus, the combination of myocardial injury and α-catenin ablation unfetters YAP, leading to increased cardiomyocyte cell cycle activity and improved recovery from myocardial injury.

These results raise the interesting possibility that modulation of intercalated disk signaling through YAP may be a means to enhance cardiac regeneration. However, many critical questions must be addressed before pursuit of such a strategy. First, this study provided scant data on the overall phenotype of either DKO or IN-DKO models, such as ventricular function, intercalated disk structure, or electric conduction. Individual fetal knockout of either αE- or αT-catenin caused cardiomyopathy. The authors did not report the functional phenotype of the DKO model, but it also likely caused ventricular dysfunction. Given these phenotypes, it is surprising that adult α-catenin inactivation in IN-DKO mice seemed to be well tolerated. This might relate to dynamic developmental remodeling of intercalated disk structure, and suggests that α-catenins are required for normal intercalated disk assembly but are dispensable for their maintenance in the adult heart. Extensive additional data are necessary to provide reassurance that modulation of intercalated disk structure in adult hearts does not cause deleterious effects. In light of potential complications of manipulating intercalated disk structure, perhaps it may be more attractive to target the mechanisms downstream of α-catenins that lead to improved myocardial outcome in IN-DKO hearts after MI. It will be necessary to establish that YAP release from α-catenin inhibition accounts for improved outcome after MI in IN-DKO and then to understand the molecular link between α-catenin and YAP activation better. Given the complex interwoven relationships between Hippo/YAP, Wnt/β-catenin signaling, and
intercalated disk integrity, it will be important to show that interventions downstream of α-catenin do not provoke deleterious, cardiomyopathic changes.

In summary, the work of Li et al. revealed a new mechanism for intercalated disk signaling, in which α-catenin modulates the subcellular localization and transcriptional activity of YAP. This α-catenin trap restrains YAP-driven cardiomyocyte proliferation, and conceivably springing YAP from this trap will be a useful strategy to increase cardiac repair and regeneration.

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References
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