Hippo Activation in Arrhythmogenic Cardiomyopathy

Yong Hu, William T. Pu

Arrhythmogenic cardiomyopathy (AC) is an inherited heart muscle that affects 1 to 2 in 5000 individuals and accounts for 15% to 25% of cases of sudden cardiac death in patients <35 years. The cardiomyopathy is characterized by risk for lethal ventricular arrhythmias, ventricular enlargement and dysfunction, and fibro-fatty replacement of cardiomyocytes. Curiously, the disease often disproportionately involves the right ventricle and hence also has been referred to as arrhythmogenic right ventricular cardiomyopathy.

In this issue of Circulation Research, Chen et al link desmosome disruption in AC to perturbation of another key intracellular signaling pathway, the Hippo/YAP pathway (Figure).

The molecular genetics of AC indicate that it is a disease of the desmosome, intercellular junctional complexes found in epithelium and in muscle tissue. In heart, desmosomes are concentrated at the intercalated discs (IDs) that join the ends of cardiomyocytes. Breakthrough work by McKoy et al identified a frameshift mutation in the desmosome protein plakoglobin (PG, also known as JUP) as the cause of Naxos disease, a rare, autosomal-recessive form of AC. Subsequently, ~60% to 65% of more typical autosomal-dominant forms of AC were found to be because of mutations in genes encoding other components of the desmosome, including Plakophilin-2 (PKP2), Desmoglein-2 (DSG2), Desmocollin-2 (DSC2), and Desmplakin (DSP).

How does disruption of desmosomes lead to ventricular dysfunction, fibro-fatty replacement of myocytes, and a proarrhythmic substrate? Initial studies focused on the structural consequences of weakened intercellular adhesions and disruption of intercellular contacts (Figure). More recent studies also examined the effect that disruption of desmosomes has on intracellular signaling. A common feature of AC mutations is that they diminish PG localization to IDs.

Indeed, AC mutations cause PG to localize to the nucleus. Intriguingly, PG is also known as γ-catenin and has 69% amino acid identity with its better known cousin β-catenin. In addition to participating in intercellular adhesion, β-catenin is also well known for its role as a transcriptional coactivator of the canonical Wnt signaling pathway. Wnt/β-catenin signaling is a key regulator of myogenesis versus adipogenesis. In AC, nuclear PG has been proposed to contribute to AC pathogenesis by suppressing canonical Wnt signaling and thereby enhancing adipogenesis driven by PPARγ and C/EBPα (Figure).
activate the transcriptional activity of YAP-TBX5 transcriptional complexes, introducing a further mode of crosstalk between the Wnt and Hippo pathways.

Because of the reported crosstalk between Wnt/β-catenin and Hippo/YAP signaling pathways, Chen et al. investigated the Wnt/β-catenin signaling pathway in AC. In human AC myocardium, total β-catenin levels were unchanged, but it was no longer well localized to IDs. Phosphorylated β-catenin (inactivated β-catenin targeted for degradation) was higher in AC myocardium. Similar changes in β-catenin levels were also observed in murine AC myocardium, although it remained localized to IDs in these models. Altered YAP or β-catenin localization to the nucleus was not detected by immunofluorescent staining of human or murine AC myocardium, although this method can be insensitive to reduction of a weak signal. Indeed, transcriptomic analysis was consistent with reduced Wnt/β-catenin transcriptional activity. These data suggest a somewhat paradoxical situation in which...
Hippo kinase activation? The study of Chen et al.

Among them: (1) What AC genotypes are characterized by adipogenesis in AC.

The study of Chen et al. identified a new potential source of crosstalk between Wnt/β-catenin and Hippo/YAP signaling pathways in AC, namely the formation of protein complex(es) between YAP, PG, and β-catenin. Immunoprecipitation of YAP co-precipitated both β-catenin and PG. However, whether these proteins exist in 1 complex or in distinct complexes, and the subcellular localization of these complexes, remains to be determined. The functional significance of the newly described YAP-PG interaction with respect to Hippo/YAP or Wnt/β-catenin signaling likewise requires further study.

To assess the functional significance of Hippo signaling on the development of AC phenotypes, Chen et al. evaluated HL-1 cells with shRNA-mediated knockdown of PKP2 and LATS1/2. PKP2 knockdown promoted formation of intracellular fat droplets and increased the fraction of cells expressing the adipogenic transcription factor PPARγ. These effects were antagonized by knockdown of the Hippo kinases. Thus, these data are consistent with Hippo kinase activation promoting adiopogenesis in AC.

Like all scientific advances, the study raises new questions. Among them: (1) What AC genotypes are characterized by Hippo kinase activation? The study of Chen et al. unfortunately did not disclose the AC genotypes of the myocardial samples studied. Are these findings observed in all patients with desmosomal gene mutation? How about those patients with AC and without identified desmosome gene mutation? More information is also needed to determine the heart disease stage associated with Hippo kinase activation. The human samples used in this study were from patients with advanced AC, whereas the relationship of disease severity to Hippo kinase activation was not systematically interrogated in the murine models. (2) How does Hippo kinase activation influence AC phenotypes (arrhythmogenesis; lipogenesis; myocardial fibrosis impaired cardiac contraction) in vivo? Although the study of Chen et al. demonstrated activation of Hippo kinases and YAP phosphorylation in human AC and murine AC models, its pathogenic consequences in AC await further investigation. (3) What is the cardiac cell type that gives rise to adipocytes? Although transdifferentiation of cardiomyocytes is altered differentiation of cardiac progenitor cells in adipocytes of arrhythmogenic right ventricular cardiomyopathy. (4) What is the functional crosstalk between Wnt/β-catenin and Hippo/YAP pathways in AC, and how does this crosstalk contribute to the molecular pathogenesis of this disease? Does this crosstalk mediate changes in β-catenin localization and phosphorylation in AC, as described by Chen et al? (5) What is the nature and role of complex(es) containing PG, YAP, and β-catenin? Does PG interact simultaneously with both YAP and β-catenin, or are the complexes mutually exclusive (and competitive)? How do these complexes affect Wnt/β-catenin signaling? How do they affect YAP signaling through its partner transcription factors TEAD or TBX5? Do these complexes have nontranscriptional roles, for example, do they modulate signaling at adhesion junctions?

In summary, the work of Chen et al. highlights the key signaling role of IDs in cardiomyocytes and mechanistically links desmosome disruption to Hippo signaling through a novel upstream Hippo regulatory mechanism. It identifies a novel new PG–YAP interaction that may connect desmosomes to both Hippo/YAP and Wnt/β-catenin signaling pathways. In doing so, the study opens exciting new avenues to understand the pathogenesis of this enigmatic disease.

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References


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