Lin et al reveal how Yes-associated protein activates cardiomyocyte proliferation.

Signaling via the Hippo kinase cascade results in the nuclear localization and activation of transcriptional co-activator YAP (Yes-associated protein). The Hippo-YAP pathway promotes cardiomyocyte proliferation in the developing fetal heart and, when over-expressed, in adult cardiomyocytes as well. The transcriptional targets of YAP that control proliferation, however, remain largely unknown. To identify the targets of this pathway, Lin and colleagues performed genome-wide chromatin immunoprecipitation experiments with YAP as well as genome-wide transcriptional profiling of cells that had a gain or loss of function of YAP. The results obtained from these experiments revealed a total of 26 genes that bound directly to YAP (together with its DNA-binding partner, TEAD), and showed increased or reduced transcriptional activity. Among the genes that were upregulated was pik3cb, a gene that encodes part of the catalytic subunit of the kinase PI3K, which has been found in other independent studies to drive cardiomyocyte proliferation. Lin and colleagues went on to show that YAP-induced proliferation required functional pik3cb, and that heart-specific depletion of YAP, which causes hypertrophy and heart failure in mice, could be rescued in part by boosting the expression of pik3cb. Taken together, these results indicate that increasing YAP or pik3cb expression could be a useful strategy to stimulate cardiomyocyte proliferation and thereby promote myocardial regeneration after injury.

Paulin et al identify a right ventricle-specific mechanism in pulmonary hypertension and, with it, potential biomarkers of disease progression.

Unlike systemic hypertension, which leads to left ventricular failure, pulmonary hypertension results in right ventricular failure (RVF). And even though in both conditions cardiac hypertrophy occurs as a compensatory mechanism, in RVF this brief compensation is quickly followed by a catastrophic decompensation phase and increased mortality. To investigate how RVF transitions from compensation to decompensation, Paulin and colleagues studied a rat model of pulmonary hypertension. They analyzed RVF tissue during compensation and decompensation and discovered that the latter was associated with increased inflammation and decreased expression of a right ventricular-specific transcription factor called Mrf2. Upon performing an unbiased microarray screen, they found that a number of microRNAs (miRs) were misregulated during decompensation. Among the down-regulated miRs was miR208, which normally suppresses expression of a transcription factor called Mrf2. Upon performing an unbiased microarray screen, they found that a number of microRNAs (miRs) were misregulated during decompensation. Among the down-regulated miRs was miR208, which normally suppresses expression of a transcription factor called Mrf2. Thus the downregulation of miR208 in compensation could increase MED, which in turn could further suppress the already diminished Mrf2. Exactly how these factors contribute to RVF remains to be determined, but in the meantime these changes could serve as valuable biomarkers of disease progression.

Alpha-catenins suppress YAP and reduce proliferation in cardiomyocytes, report Li et al.

Like Lin and colleagues, Li and colleagues have been studying the control of cardiomyocyte proliferation by the transcriptional co-activator YAP. But whereas Lin and colleagues searched for downstream targets of YAP, Li and colleagues have identified α-catenins as upstream regulators. Inside cells, α-catenin proteins link the junction proteins, cadherins, to the cytoskeleton, but aside from this structural role, α-catenins have been found, in some cell types, to control proliferation. It is thought that, through their interaction with the cadherin junctions, the α-catenins sense an increase in cell density and shut down cell division. Li and colleagues now show that this anti-proliferative effect also occurs in the heart. Specifically, they found that mouse hearts lacking the two types of α-catenin exhibited an approximately 23% increase in cardiomyocyte number. They also found that phosphorylation of YAP was reduced in the catenin-deficient hearts, which prevented YAP from entering the nucleus and activating proliferation genes. The team went on to show that compared with their wild-type counterparts, the mice lacking α-catenin displayed improved repair of heart tissue following myocardial infarction. The discovery lends further support to the notion that the activation of YAP could be a potential regenerative therapy.