Research

Disease Modeling and Therapeutics for heart diseases

My research aims to understand the underlying molecular and cellular mechanisms that underpin disease progression of the human heart and lung, and to develop novel screening platform for the evaluation of potential therapeutic intervention. At present, most drug screening processes involve screening a single cell type against a large number of compounds using defined biochemical assays in a high throughput format. However, such chemical screens often overlook the effects of a drug on an organism, which is complex and involves interactions at multiple levels that cannot be predicted using simple biochemical assays. Thus, recapitulation of the in vivo cellular microenvironment would provide a more biologically relevant surrogate to predict the response of the organism. Currently, the main research areas include the followings:

a) Therapeutics development to enhance adult cardiomyocyte proliferation after myocardial infarction.
b) Examination of cardiac phenotypes in other disease models.
c) Genetic manipulation of key genes governing cardiac or pulmonary diseases, and screening for potential therapeutics.

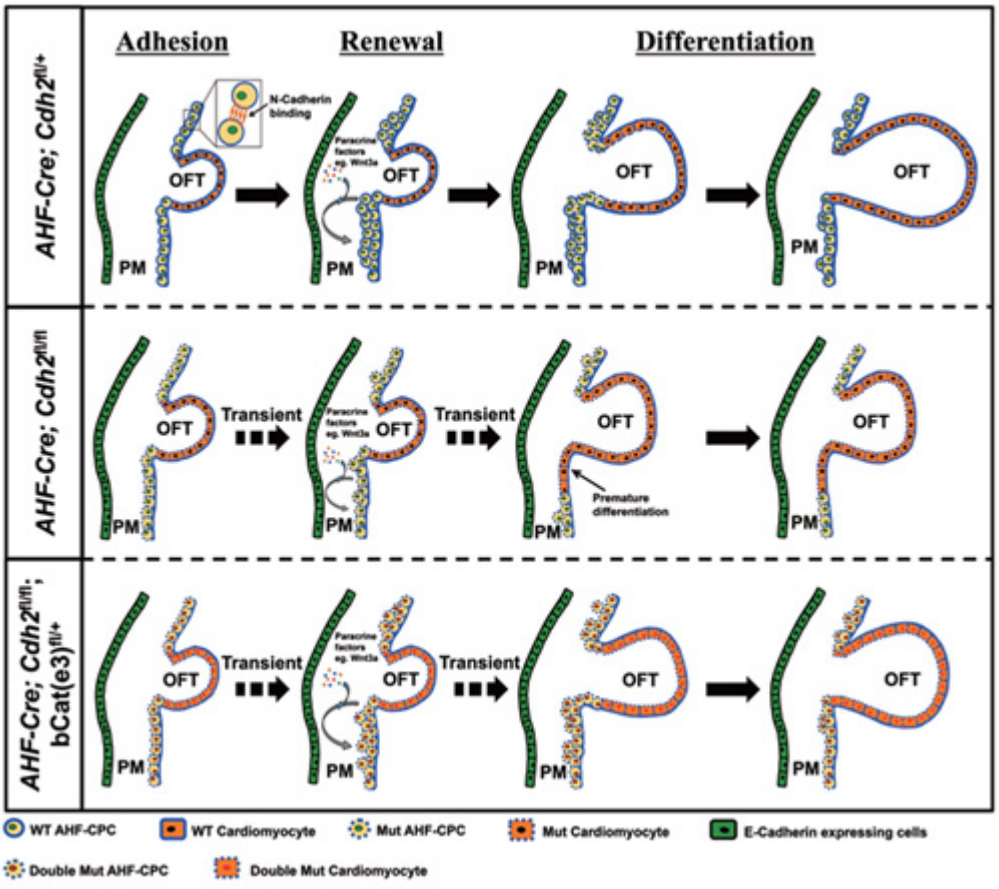

Figure legend: Schematic summarizing the role of N-cadherin in the maintenance of anterior heart field cardiac progenitor cells (AHF-CPC).

In wild-type mice, N-cadherin expression by CPCs allows the cells to be properly adhered in the microenvironment of the pharyngeal mesoderm, thereby allowing the cells to be sufficiently exposed to paracrine factors that promote multipotency and proliferation. In addition, N-cadherin serves to maintain β-catenin levels by sequestering the molecules at the cell membrane. These allow the AHFCPCs from wild-type mice to achieve higher Wnt signaling activity as compared to single mutant (AHF-Cre;Cdh2fl/fl), where an overall downregulation of Wnt signaling activity was observed, which consequently resulted in premature differentiation of CPCs to cardiomyocytes in the AHF. Expectedly, activating Wnt signaling by overexpression of β-catenin in the double mutant (AHF-Cre; Cdh2fl/fl; bCat(e3)fl/+) was able to partially rescue the premature differentiation phenotype of the CPCs observed in Cdh2 single mutant.