Metabolic mechanism for cardiomyocyte cell cycle arrest

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The mammalian heart undergoes maturation during postnatal life to meet the increased functional requirements of the adult. However, the key drivers of this process remain poorly defined. We are currently unable to recapitulate postnatal maturation in human pluripotent stem cell-derived cardiomyocytes, limiting their potential as a model system to discover regenerative therapeutics. Here, we provide a summary of our studies where we developed a 96-well device for functional screening in human pluripotent stem cell-derived cardiac organoids. Through interrogation of >10,000 organoids, we systematically optimize parameters, including extracellular matrix, metabolic substrate and growth factor conditions that enhance cardiac tissue viability, function and maturation. Under optimized maturation conditions, functional and molecular characterization revealed that a switch to fatty acid metabolism was a central driver of cardiac maturation. Under these conditions cardiomyocytes were refractory to mitogenic stimuli and we found key proliferation pathways including β-catenin and YAP1 were repressed. This proliferative barrier imposed by fatty acid metabolism in cardiomyocytes could be rescued by simultaneous activation of both β-catenin and YAP1 using genetic approaches or a small molecule activating both pathways. These studies highlight that human organoids coupled with higher throughput screening platforms have the potential to rapidly expand our knowledge of human biology and potentially unlock novel therapeutic strategies.