Getting to the heart of the heart

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Helping to change scientists' thinking about how the heart is formed, investigators at Children's Hospital Boston have identified a type of stem cell that gives rise to at least two different cell types that make up the heart's tissues. The findings, to be published in the Dec. 15 *Cell*, bring researchers a step closer to being able to regenerate tissues to repair congenital heart defects in children and damage caused by heart attacks in adults.

Working in parallel, a separate team at Massachusetts General Hospital discovered a related progenitor cell that gives rise to the right-sided heart chambers, forming myocardial cells, smooth muscle cells, and endothelial cells.

Since these different cell types were thought to have separate ancestors, the studies offer a new understanding of the development of the mammalian heart – the earliest organ to develop, and the one most susceptible to congenital defects. They also bring researchers a step closer to being able to regenerate tissues to repair congenital heart defects in children and damage caused by heart attacks in adults.

The two laboratories are now trying to determine the relationship between the two types of progenitor cells discovered. Both papers will appear in the December 15 issue of the journal *Cell*, which was published online November 22.

The Children's team, led by senior investigator Stuart H. Orkin, MD, a Howard Hughes Medical Institute investigator, and Sean Wu, MD, PhD,

the study's first author, first worked with mouse embryonic stem cells in culture. They allowed the cells to differentiate in a Petri dish, then isolated a relatively rare subtype of cell (just 1 percent of the cells in the dish) that were poised to begin developing along a cardiac pathway. The presence of these cardiac progenitors was indicated by a green fluorescent protein, which lit up when a gene called Nkx2.5 was activated. Orkin and Wu then showed that these cells further differentiated into both myocardial cells and smooth-muscle cells.

Next, using the same fluorescent "tags," Orkin and Wu isolated the same cardiac progenitor cells directly from live mice early in embryonic development.

"There have been a number of publications about stem-like cells in the heart, but these are the first studies to identify such cells during embryonic development, and to show that they give rise to different cell types," says Orkin, who is the David G. Nathan Professor of Pediatrics at Harvard Medical School and also chairs the department of pediatric oncology at Dana-Farber Cancer Institute. He and Wu are also members of the Harvard Stem Cell Institute.

"Previously, it had been thought that each cell type in the heart had a different origin. Now, it's pretty clear that some have common origins," Orkin adds. "This changes the notion of how the heart develops. Instead of multiple different cell types migrating and coming together to form the heart, the heart comes from stem cells that give rise to multiple cell types in the same local environment – a simpler way of building the organ. And because these cells can make multiple cell types, they could be more useful in repairing the heart than any single kind of cell."

Orkin cautions that there are many steps before cardiac progenitor cells could be used to repair a human heart. The studies were done in mice, and it's still unknown what factors make embryonic stem cells

differentiate into cardiac progenitors, or what factors make cardiac progenitors differentiate into more specialized heart cells. But ultimately, cardiac surgeons at Children's hope to be able to use cardiac stem cells to repair congenital heart defects such as defective heart valves, missing or undeveloped arteries, or underdeveloped heart chambers.

"If you understand the process of how things develop from very primitive embryonic stem cells to fully differentiated tissue, you have the potential to duplicate that process in the lab and make a tissue that a patient might need," says John Mayer, MD, a cardiovascular surgeon at Children's who is developing tissue-engineering techniques to create biological replacements for failing heart valves. Felix Engel, PhD, a cardiology researcher at Children's, recently got heart muscle cells to replicate, a feat that normally occurs only during embryonic development and represents another approach to repairing injured heart muscle. By apparently stimulating tissue regeneration, he was also able improve heart function after a simulated heart attack.

Source: Children's Hospital Boston