Uncovering the exquisite choreography of the developing human heart

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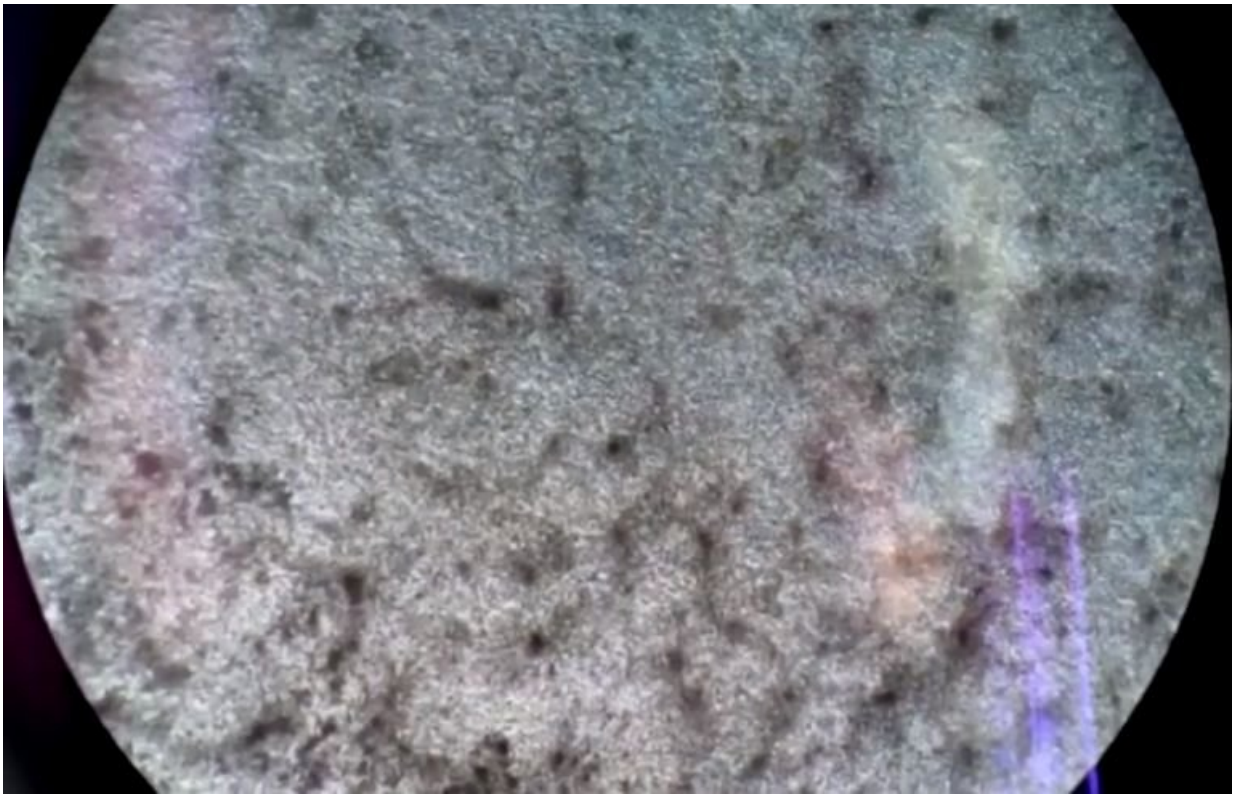

How do you mend an injured heart? We don't yet know—but the answer is likely to lie in how the heart builds itself in the developing embryo one cell at a time.

In a study published today in *Cell Stem Cell*, Australian researchers report on the most in-depth study to date of exactly how human stem cells can be turned into heart cells. The work involved measuring changes in gene activity in tens of thousands of individual cells as they move through the stages of heart development.

The upshot: an unprecedented resource that may help us find ways to repair the heart in the future.

The findings were uncovered by researchers at the Institute for Molecular Bioscience (The University of Queensland) and the Garvan Institute of Medical Research.

The problem: hearts can't fix themselves

As humans, we have the capacity to repair ourselves, but so far this has only been observed in select tissues such as the skin, liver, skeleton, and limb muscles. Unlike those tissues, the heart does not have the capacity for self-repair after damage (such as a heart attack). This is one reason why heart disease is the leading cause of death worldwide.

"The big challenge, as we see it, is to uncover new approaches and new insights into ways to help the heart repair itself," explains Dr. Nathan Palpant (Institute for Molecular Bioscience, The University of Queensland), who co-led the new research.

"We think the answers to heart repair almost certainly lie in understanding heart development. If we can get to grips with the complex choreography of how the heart builds itself in the first place, we're well placed to find new approaches to helping it rebuild after damage."

Growing a 'heart' from stem cells

To explore human heart development, the researchers chose to mimic, in the lab, how a heart develops in the embryo. They started with skin-derived human pluripotent stem cells (induced pluripotent stem cells) that are capable of giving rise to any cell type in the body. They used cues from developmental biology findings to guide the cells, over time, into heart cells (cardiomyocytes).

Tracking the destiny of every cell

The researchers next used cutting-edge technology of single-cell RNA sequencing to catalogue how individual cells changed as they made the journey from stem cells to mature heart cells. Specifically, single-cell sequencing detects the levels of RNA 'readouts' within one cell at a given time. The more copies of a RNA readout (or transcript), the more active the gene from which the RNA is transcribed.

Thus, for each of 40,000 individual heart cells, they measured the activity of about 17,000 genes—this is essentially every gene that is active in the heart.

The research reveals gene-activity patterns uniquely associated with the development of cardiac cells, and in so doing, vastly increases our understanding of how the heart builds itself.

"The development of the heart is like an intricate dance," says A/Prof Joseph Powell (Garvan), who is Head of the Garvan-Weizmann Centre for Cellular Genomics and co-led the research.

"Each cell goes through its own series of complex, nuanced changes. They are all different, and changes in one cell affect the activity of other

cells. By tracking those changes across the different stages of development, we can learn a huge amount about how different subtypes of heart cells are controlled, and how they work together to build the heart."

Uncovering the 'toggle switch' that makes the heart grow bigger

Using this new resolution of information about heart development, the team made a new discovery that the gene known as HOPX is essential for controlling how the heart grows bigger—a process known as hypertrophy.

HOPX functions like a toggle switch that controls a critical decision point in heart development: the change from heart cells that are 'immature' (and still dividing), to heart cells that no longer divide but are bigger and more mature. This finding will help researchers learn more about the processes that underlie congenital heart disease (when the heart does not develop properly) and may provide a new strategy for controlling heart regeneration.

A better way to grow heart cells

The HOPX findings also shed light on the conditions required to encourage stem cells to develop into mature heart cells. This new knowledge will support researchers to accurately and reliably grow mature heart cells in the lab, which will greatly benefit future research into heart development and disease.

New horizons in heart development and repair

"We can start to look deeper and more carefully at how the heart

develops," says Dr. Palpant. "The information we've gained from this work has positioned us to take on new and bigger questions in cardiovascular disease."

Adds A/Prof Powell, "We are now building on the knowledge gained from this work to investigate at what stages during heart development, and in what cell subtypes, the genetic risks of cardiovascular disease become most dangerous."

Provided by Garvan Institute of Medical Research