NUS National University of Singapore

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The method developed by Professor G.V. Shivashankar and his team lowers the risk of stem cells going awry when they are used to treat patients. PHOTO: COURTESY OF MECHANO-BIOLOGY INSTITUTE, SINGAPORE.

Squeezing mature cells to become stem cells

S'pore scientists' chemical-free method may open new field in regenerative medicine

Luke Anthony Tan

When an embryo is days old, its powerful embryonic stem cells grow without limit, turning themselves into any cell the body needs.

But as these cells mature, their scope is limited to the function defined for them. For years, scientists have explored ways to return mature cells into an embryonic-like, or pluripotent, state.

Research has shown that, in this state, these blank-slate cells can be rejuvenated into any cell in the body. With it, comes the promise of cures for many diseases.

The conventional processes, including one which won Japanese scientist Shinya Yamanaka the Nobel Prize for Medicine in 2012, relies on chemicals to turn mature cells into master cells.

Called induced pluripotent stem cells (iPSCs), these are typically made from mature cells using biochemical cues that genetically modify the mature cells.

But stem cells, if they cannot be controlled, can lead to cancer.

Now Singapore scientists have, for the first time, managed to turn back the clock on mature cells by putting the squeeze on them.

By confining fibroblast (connective tissue) cells to a tight space, researchers found that they naturally turned into master cells.

In the study led by Professor G.V. Shivashankar, deputy director at the Mechanobiology Institute at the National University of Singapore and the Firc Institute of Molecular Oncology in Italy, the iPSCs were made using only mechanical cues from the mature cells' environment.

Said Prof Shivashankar: "In our work, we've been looking at how cells are affected by the local mechanical cues they would receive in the body... And this study shows that cells have this ability to reverse themselves (into stem cells), driven by mechanical constraints, and we can actually make induced pluripotent stem cells out of these constraints."

Because chemicals are not used in this process, there is less risk of cells going awry when they are one day used to treat patients, the scientists believe.

To make these iPSCs, a single fibroblast cell from a mouse was allowed to grow on "islands" of confined spaces in a culture dish.

Based on past research, the scientists knew that these cells, when grown on confined areas, quickly assume the area's shape, stretching and adhering to the defined area.

In doing so, Prof Shivashankar explained that the cells would be in a "mechanically stressed" state.

But as the cell multiplies over the next few days, the cells eventually run out of space and begin to grow on top of one another, forming a spherical cluster of cells – of as many as 100.

At this stage, the cells have become "mechanically relaxed", Prof Shivashankar said, and this causes the packaging of the cells' DNA to become more "loose", a sign that the cells are becoming more stem cell-like. By the sixth day, the fibroblast cells start to lose their original genetic traits. On the 10th day, they start to express genetic patterns unique to stem cells, the researchers found.

Dr Xia Yun, an assistant professor at Nanyang Technological University's Lee Kong Chian School of Medicine, said Prof Shivashankar's study is an important "missing piece of a jigsaw puzzle" and it may open an entirely new field in regenerative medicine.

"Since the establishment of Yamanaka's reprogramming method, tremendous effort has been dedicated to discovering a less aggressive reprogramming approach that does not involve gene transduction (manipulation)," said Dr Xia, who is also the principal investigator at the school's Stem Cell Lineage Specification and Organ Regeneration Laboratory.

"This study is the first to describe that biophysical factors alone can change the epigenetic (how genes are used) landscape of mouse fibroblasts, leading to the reprogramming towards a stem-like cellular status," she added.

As for future plans, Prof Shivashankar said he and the six other researchers in his team hope to use their new technique to better understand how cancer cells can become cancer stem cells, since genetically modified iPSCs are known to turn into tumours in the human body.

"Our breakthrough findings will usher in a new generation of stem cell technologies for tissue engineering and regenerative medicine that may overcome the negative effects of genomic manipulation," he added.

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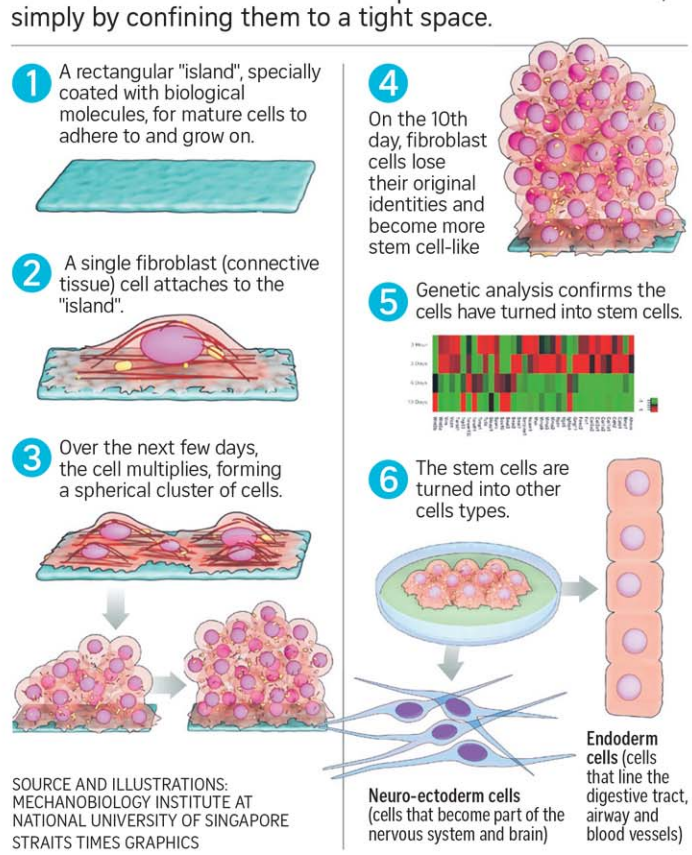
NEW TECHNIQUE

Our breakthrough findings will usher in a new generation of stem cell technologies for tissue engineering and regenerative medicine.

PROFESSOR G.V. SHIVASHANKAR

Physically rewiring mature cells into stem cells

Conventionally, scientists use chemicals to turn mature cells into induced pluripotent stem cells (iPSCs) - cells that have the potential to become any cell type of the body. However, in new research, mature cells can be physically rewired into stem cells without exposure to biochemicals, simply by confining them to a tight space.



SOURCE AND ILLUSTRATIONS: MECHANOBIOLOGY INSTITUTE AT NATIONAL UNIVERSITY OF SINGAPORE
STRAITS TIMES GRAPHICS

Types of stem cells and their uses

WHAT ARE STEM CELLS
Stem cells are the blank-slate cells of the body.

In early embryos, they form the foundation for all the cells of the adult body; in adults, they replenish lost cells and tissue.

Broadly, there are two types of stem cells in humans: embryonic and adult.

EMBRYONIC STEM CELLS
As their name suggests, embryonic stem (ES) cells are derived from embryos, and can develop into more than 200 cell types of the adult body.

However, the ES cells used in research today generally come from unused in-vitro fertilisation (IVF) embryos donated for research. These embryos are derived from an egg that has been fertilised in the laboratory, and the donor of the egg has given informed consent for its use in research.

Scientists have found that under certain conditions, ES cells can produce limitless numbers of themselves, making them useful for both research and regenerative medicine.

ADULT STEM CELLS
Scientists have identified adult stem cells in many organs and tissues such as the brain, bone marrow, skin, heart and more.

These stem cells remain quiescent (non-dividing) for long periods of time until the body requires more cells to replace dead or damaged tissue.

Typically, there is a very small number of stem cells in each tissue which can produce only certain types of cells.

For example, a stem cell derived from the liver can only make more liver cells.

INDUCED PLURIPOTENT STEM CELLS
While embryonic and adult stem cells occur naturally, scientists have produced stem cells from mature body cells in the laboratory.

These stem cells are called induced pluripotent stem cells (iPSCs).

Scientists hope that iPSCs can pave the way for regenerative and personalised medicine, since iPSCs made from a patient's mature cells, for example, could potentially be used to replace or repair his damaged or diseased tissue.

Although iPSCs can give rise to different cell types, just like ES cells can, scientists are unsure if iPSCs and ES cells have any significant differences in clinical use.

Still, such stem cells are useful tools for drug development and to study diseases, and scientists believe continued research on iPSCs will help uncover ways to make iPSCs for regenerative and personalised medicine.