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Research on stem cells transforming sciences

With series of advances, the underlying principles of basic biology are in the process of being rewritten

By Carolyn Y. Johnson | GLOBE STAFF FEBRUARY 17, 2014

The discovery shocked researchers in its simplicity — could a weak acid bath really be all that was required to trigger a mature blood cell to transform into powerful stem cells?

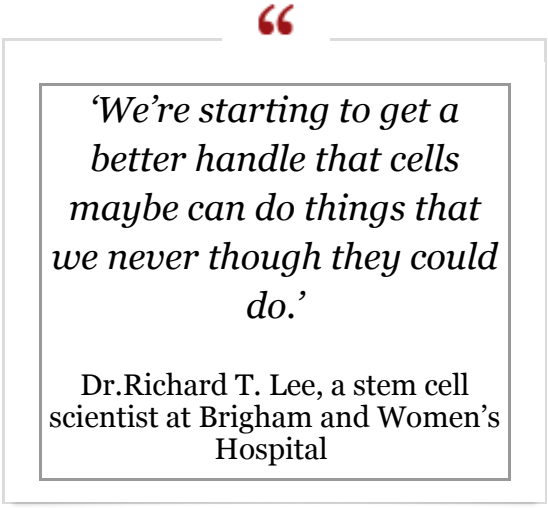
But the underlying insight that a specialized cell can easily shapeshift into something completely different is just the latest remarkable contribution to a revolution in how scientists think about life's building blocks.

Stem cell biology is often depicted as a field offering medical promises yet to be fulfilled — the near-miraculous potential to one day repair spinal cord injuries or treat heart failure. Focusing on regenerative medicine's thus-far-minuscule impact on patient care, however, misses what scientists have already wrought: a shift in our understanding of cells so radical that it has rewritten the rules of biology in less than a generation.

Even normal cells appear to contain a capacity for regeneration far more powerful than anyone knew. This new idea is opening up profound, almost philosophical questions about why cells would have this capacity, as well as opportunities to study

cells that go awry in disease and to one day use patients' own cells to heal them.

"It's slowly changed how we think about life, and I know that sounds grandiose, but it's not grandiose at all," said Dr. Richard T. Lee, a stem cell scientist at Brigham and Women's Hospital, where other researchers devised the surprising new method of creating stem cells that was announced last month. "We're starting to get a better handle that cells maybe can do things that we never though they could do."



Undergraduates routinely do experiments in their laboratory classes that would have seemed like science fiction a decade ago, such as turning stem cells into nerve cells found in the spinal cord that are involved in movement.

Lee, who has recently focused on identifying ways to turn aging heart muscle young again, admits that the projects he is working on in his laboratory today would have seemed "nuts" just five years ago.

If the new finding holds up and is easily repeated by other laboratories, it will be yet another sea change.

For years, the dogma was that mature cells have fixed identities: Skin is skin, muscle is muscle, liver is liver. The predominant view was that early in development, organisms start out with versatile stem cells, which become the multiple kinds of cells in the body, and that this was basically a one-way road — there was no going back from a specialized cell to a stem cell.

But the last decade has been a continual lesson in how that notion is wrong. Cells can be induced to revert to a more basic state by adding a cocktail of four genes, scientists found in 2006 — a discovery that shared the Nobel Prize in 2012.

Scientists have also discovered an increasing number of ways to skip the trip back to a stem cell-like state and directly convert one mature cell type into another, such as changing one type of mouse pancreatic cell into the type that makes insulin.

The recipe for creating stem cells from mature cells or changing cell types has continually gotten simpler and safer for potential therapeutic use, with a team reporting last year that they could trigger the change without using viruses to insert genes into a cell, which raises the risk of cancer.

Even for scientists in the midst of pushing these various technologies forward, it can be startling to take a step back and remember how quickly notions about what is possible have changed.

“It’s unbelievable. I teach undergraduates at Harvard, and it’s like normal, assumed knowledge — they don’t blink. These cells can turn into these other cells. That’s normal” to them, said Paola Arlotta, an associate professor in the department of stem cell and regenerative biology at Harvard University. “They grew up in these years, where these things can happen.”

So while the report by Boston and Japanese scientists in late January that a simple environmental stress was enough to turn mature cells back into stem cells is a radical idea, it is in keeping with other upheavals now accepted as fact.

Few scientists will feel confident that the simple acid-bath technique will work to create stem cells until other laboratories repeat the experiment, which many researchers are already trying to do.

But, to varying degrees, scientists are open to the possibility that it works — in part because time after time, research has shown how malleable cells really are.

Konrad Hochedlinger, a stem cell scientist at Massachusetts General Hospital and Harvard, said that he’s not as skeptical as some of his colleagues because he has had the experience of being surprised by biology.

Early in his career, Hochedlinger was one of the scientists racing to identify factors that could be added to a mature cell to trigger its return to a stem cell-like state.

He recalls the wide range of techniques tried, such as fusing cells of different types together. They also tried adding many molecules to cells.

In 2006, a Japanese scientist, Dr. Shinya Yamanaka, showed it took only four genes to make embryonic-like stem cells that they called induced pluripotent, or iPS, cells.

"Everyone was surprised. Now, everyone accepts it as, 'Yeah, of course, iPS cells were always there,' " Hochedlinger said. "I thought it would require dozens if not hundreds of molecules. . . . That's part of the reason I try to keep an open mind, even though I am also surprised by this acid finding. I'm open to the possibility this is really possible."

There's natural caution. The field is so new and so hot that it has been burned in the past by exciting results that turned out to not be easily repeatable, or to have been generated by flawed experiments. But many are hopeful that the new finding will turn out to be true, because it will open up new mysteries to pursue about cells' capabilities.

Why would it be so easy for cells to revert back to a primitive state in the first place? Does it naturally happen in the body? If it's relatively easy, does the real question become how nature keeps cells from changing most of the time?

If the field is ever going to build new, functioning organs or cells to replace sick brain cells, scientists will need to know that secret, too.

"It's actually a really sort of spooky time," Lee said. "Because I think that there's this excitement and worry at the same time — excitement over the things we can do, but worry about how to do them and how to control them so that we can really make good on the promises."

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