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Decades of College Dreams

Cells reprogrammed in living mice

By Gretchen Vogel

Researchers have discovered a surprisingly effective way to "reprogram" mature mouse cells into an embryolike state, able to become any of the body's cell types. Their recipe: Let the transformation happen in a living animal instead of a petri dish. The finding could help scientists better understand how reprogramming works and it may one day help breed replacement tissues or organs in the lab-or in patients.

In culture dishes, ramping up the expression of just four genes can turn skin and other cells into so-called induced pluripotent stem (iPS) cells. Pluripotent cells can become any of the cell types usually found in the body-although there are certain special types of tissue, such as placenta, that they can't form. (Stem cells extracted from embryos, called embryonic stem [ES] cells, are also pluripotent.)

Many scientists had assumed, however, that the cellular environment in living tissues would interfere with the reprogramming process, especially because natural development is usually a one-way street, from stem cells to differentiated and mature tissue cells. "The assumption is that everything in our body is promoting differentiation," says Manuel Serrano of the Spanish National Cancer Research Center in Madrid.

Serrano and his colleagues have proved that assumption wrong. They developed transgenic mice in which a specific drug can turn on the four repro-gramming factors in all the animals' cells. The first attempts to induce reprogramming killed the animals within days as their intestines failed, Serrano says. A lower dose of the drug was not immediately lethal, the scientists reported Wednesday in Nature, but the animals developed tumors that arise from pluripotent cells called teratomas. The teratomas were unusual, however. They also included placental cells, which standard iPS and ES cells can't produce. Two mice also developed cysts in their abdomen that resembled very early embryos, with a yolk sac and the first signs of blood cell development.

That suggests that the cells have gone beyond pluripotency and taken on some characteristics of totipotent cells, which are even more developmentally primitive and can produce not only embryonic tissues, but also the supporting tissues such as placenta. (A fertilized egg is the classic example of a totipotent cell.) Reprogramming in living tissues is not only possible, "it's even better" than in a culture dish, Serrano says.

"The paper really is quite striking and provocative (if a little creepy)," writes George Daley, a stem cell researcher at Boston Children's Hospital and Harvard Medical School in Boston, in an email. Both he and Serrano say it's still unclear why reprogramming inside the mouse body pushes cells further back toward a primitive state. Figuring that out could help researchers better understand what happens as cells are reprogrammed and may also provide new clues to the molecular signals that control the difference between pluripotency and totipotency.

Although the growth of the tumors in the mice was uncontrolled, Serrano says he and his colleagues want to test whether a more limited version of in vivo reprogramming might enable injured tissues, such as the heart, to regenerate. They also want to see if they can use a variation of the technique to reprogram human cells placed inside a mouse.

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Human ES and iPS cells seem to be at a slightly more differentiated state than their mouse counterparts, which makes it more difficult to grow certain types of cells from them. Reprogramming in vivo might allow scientists to isolate more primitive-and more flexible-human pluripotent cells, Serrano says.

Daley notes that when amphibians regenerate their limbs, they form a cluster of primitive undifferentiated cells called a blastema. Perhaps a version of in vivo reprogramming could allow mammals to regenerate tissues that they usually can't regrow, such as limbs or heart, he says: "I think that's certainly an interesting possibility."

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