STEM CELLS

Reprogrammed Cells Come Up Short, for Now

Stem cell research offers an ever-shifting battlefield, with vested interests and biologists squabbling over the political, ethical, and scientific merits of different types of cells. Some of the fiercest skirmishes once took place between advocates and opponents of fetal cells. Then along came human embryonic stem cells, opening several fronts, including not-so-civil wars among hES researchers and fans of various adult stem cells. Now two recent papers have dragged the new kid on the block, induced pluripotent stem (iPS) cells, into the fray.

Those papers offer some of the first side-by-side comparisons of human iPS and hES cells as they differentiate into various kinds of cells. In both papers, researchers report that iPS cells can form desired cell types, but they do so with less efficiency than hES cells. Robert Lanza of Advanced Cell Technology, a biotech company based in Worcester, Massachusetts, who co-authored one of the studies, doesn't mince words about iPS cells: "These cells are pretty screwed up," he says.

Not so fast, say other researchers, who contend that not all iPS cells are equal. "The differences are real, but one shouldn't overinterpret them," says James Thomson of the University of Wisconsin, Madison, who is a co-author of the second paper. "When you go back and tweak the conditions, [iPS cells] seem to have the same potential" as ES cells, he says. The differences, Thomson and others explain, are probably due to imperfections in the reprogramming process that occur when scientists activate several genes to convert a differentiated adult cell into an iPS cell. "There's going to be a lot of noise" in the data as scientists work to diagnose and overcome reprogramming's weak spots, Thomson says.

The latest stem cell skirmish started on 12 February with an online paper in *Stem Cells* in which researchers including Lanza and Shi-Jiang Lu of Stem Cell and Regenerative Medicine International, another biotech company based in Worcester, compared the ability of eight human iPS cell lines and 25 hES cell lines to differentiate into several kinds of blood and endothelial cell types. In one test, the hES cells made more than 1000 times more of the desired cells than the iPS cell lines. They also found that, in contrast to cells derived from hES cells, various cell types produced by iPS cells started to undergo cellular aging and programmed death after a short time in culture. Such observations are especially worrisome, Lanza says, as scientists hope to use stem cells in industrial quantities—either for drug testing or for eventual cell therapies. (Most of Advanced Cell Technology's intellectual property portfolio focuses on ES cells and nuclear transfer techniques.)

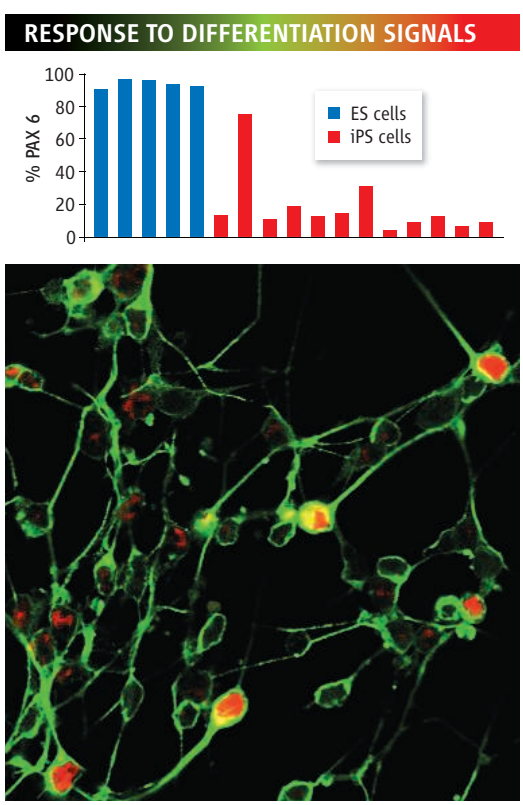
In the second study, Su-Chun Zhang, Thomson, and their colleagues at the University of Wisconsin, Madison, compared the differentiation of hES and iPS cells into neuronal cells. The two stem cell types behaved very similarly as they became neurons and glia, expressing the same genes at the same time, the researchers reported online 16 February in the *Proceedings of the National Academy of Sciences*. And both hES- and iPS-derived cells acted like normal brain cells in lab tests. But more than 90% of the hES cells responded to the chemical recipe for making neural cells, whereas the iPS cells' response was more variable: In some lines, only 15% of cells turned into neuronal cells, in another, 79%.

In contrast to the Wisconsin group's results, Hans Schöler, a stem cell biologist at the Max Planck Institute for Molecular Biomedicine in Münster, Germany, says he and his colleagues have noticed no differences between ES and iPS cells as they differentiated into neural stem cells. But, he adds, a member of his lab did try unsuccessfully for nearly 3 years to prompt murine iPS cells to form a healthy live-born mouse—the ultimate test of pluripotency that mouse ES cells achieve without a problem. Other groups succeeded, but the efficiency was still low, he notes. In addition, several groups have already reported differences in global gene expression between hES and human iPS cells.

Such observations highlight that cellular reprogramming is still an inexact science. Like Thomson and other stem cell scientists, Schöler thinks that incomplete reprogramming still mars many iPS cells. The first iPS techniques involved using viruses to insert extra copies of reprogramming genes into target cells, but the inserted genes may affect the cells' behavior after reprogramming. Indeed, Lanza says that more-recent studies by his colleagues suggest that cells reprogrammed with newer virus-free techniques are better at differentiating.

Shinya Yamanaka of Kyoto University in Japan, who was the first to successfully reprogram mature mouse cells into iPS cells, says that he has also observed that the differentiation performances of iPS and hES cells vary from line to line. But his lab has not seen systematic differences between the cell types. He and his colleagues are searching for a way to accurately identify more fully reprogrammed iPS cell lines. He predicts that adding additional factors to the reprogramming mix should produce more dependable iPS cells.

Clearly, these findings do not settle the debate, says Miodrag Stojkovic of the Prince Felipe Research Centre in Valencia, Spain "We're all very excited to work with iPS cells," he says. "But first the science has to determine how they are similar and what is different." **–GRETCHEN VOGEL**



Work in progress. iPS cells can differentiate into functional neurons (*above*), but analysis of PAX6 gene expression shows they are less responsive than human ES cells to neuron-making cues (chart).

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