Science

Stem Cell Research: A Snapshot of the Science

This past quarter, several papers were published that give us a good snapshot of the state of the science of stem cell research. First, there were three papers that continue to highlight the importance of techniques to directly reprogram one cell type directly to another cell type without the need for a stem cell intermediate.

Scientists at the Salk Institute in La Jolla, California, report that they have been able to transform human skin cells directly into the transplantable white blood cells that protect patients from infections and other invaders.[1] This direct reprogramming process—called indirect lineage conversion—only took two weeks, which is significantly shorter than the two months needed to reprogram skin cells into induced pluripotent stem cells (iPSCs). Significantly, the new method generates cells that engraft well and do not produce tumors in mice. It is also a relatively simple method that only requires two reprogramming molecules called SOX2 and miRNA125b. Induced pluripotent stem cell technology originally required four reprogramming molecules.

In an independent study, researchers at Boston's Children's Hospital have reprogrammed mouse blood cells into the specialized blood-forming hematopoietic stem cells (HSCs) that could be used for bone marrow transplants.[2] Again, this process circumvented the need for pluripotent stem cells. HSCs usually reside in the bone marrow, but they are rare, comprising about one in every twenty thousand cells in the marrow. The scientists first identified thirty-six molecules that turn genes on and off in HSCs. They then narrowed these transcription factors down to eight

[1] Julian Pulecio et al., "Conversion of Human Fibroblasts into Monocyte-Like Progenitor Cells," *Stem Cells* 32.11 (November 2014): 2923–2938.

[2] Jonah Riddell et al., "Reprogramming Committed Murine Blood Cells to Induced Hematopoietic Stem Cells with Defined Factors," *Cell* 157.3 (April 24, 2014): 549–564.

molecular factors to robustly reprogram blood progenitor cells into these induced HSCs. These iHSCs were able to regenerate all the cells of the blood. Significantly, the gene expression profile of the induced HSCs was indistinguishable from that of the normal HSCs suggesting that they will function normally if they are transplanted into patients who need to rebuild either their circulatory or their immune systems.

Finally, investigators at Columbia University's Naomi Berrie Diabetes Center have transformed human gut cells into insulin-producing cells by simply turning off a single gene called FOXO1.[3] This experiment builds on work published several years ago that had shown that mouse intestinal cells could be transformed into insulin-producing cells and that these cells could normalize blood glucose levels in diabetic mice. In this recent paper, the team demonstrated that human intestinal cells lacking FOXO1 began to release insulin in response to glucose. Now, the scientists will need to identify a drug that could be given to diabetic patients to transform some of their gut cells into these insulin-producing cells.

Next, there were two research papers that continue to highlight both the power and the limits of induced pluripotent stem cell technology. First, in a beautiful manuscript published in the premier scientific journal *Cell*, Han Qin et al. report that they have identified several, both known and previously unknown, biochemical pathways that usually prevent cells from being reprogrammed into the pluripotent stem cell state.[4] Removing these genetic barriers to reprogramming significantly increased the efficiency of producing iPSCs. Intriguingly, the biologists propose that these genetic barriers are normally in place to help the mature cell in the organism, say the heart cell or the blood cell, to maintain its identity and functional role. These genes also work to prevent adult cells from becoming cancer cells. This study brings physicians one step closer to realizing the promise of using iPSC technology to both routinely and easily generate cells and tissues for transplantation.

Second, a team of Korean researchers has described the reversion of iPSC-derived cells back into a pluripotent state.[5] After developing neural stem cell lines from iPSCs, the scientists noticed that some of these cell lines spontaneously returned to the pluripotent state about four weeks after they were first established. Importantly, fully committed and differentiated nerve cells generated from the iPSCs did not regain pluripotency. Only the nerve precursor cells did. This data indicates that scientists and physicians will now have to worry about the possibility that iPSC-derived therapeutic products may regain their pluripotency within a patient's body. This would be a potentially dangerous scenario for the patient because pluripotent stem cells could engender tumors.

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[3] Ryotaro Bouchi et al., "FOXO1 Inhibition Yields Functional Insulin-Producing Cells in Human Gut Organoid Cultures," *Nature Communications* 5 (June 30, 2014), doi: 10.1038/ncomms5242.

[4] Han Qin et al., "Systematic Identification of Barriers to Human iPSC Generation," *Cell* 158.2 (July 17, 2014): 449–461.

[5] Hyun Woo Choi et al., "Neural Stem Cells Differentiated from iPS Cells Spontaneously Regain Pluripotency," *Stem Cells* 32.10 (October 2014): 2596–2604.

In the end, I predict that the direct reprogramming methods from one mature cell type into another mature cell type that could be used for therapeutic purposes will make pluripotent stem cell technology obsolete in the not so distant future. This would make the potential problems associated with both embryonic and induced pluripotent stem cell technologies moot.

Cachexia and End-of-Life Care

Hospital ethicists are often faced with the question of withdrawing assisted nutrition and hydration (ANH) from patients who are imminently dying. The *Ethical and Religious Directives for Catholic Health Care Services* directs physicians to provide ANH to patients until they "become morally optional when they cannot reasonably be expected to prolong life or when they would be 'excessively burdensome for the patient or [would] cause significant physical discomfort, for example resulting from complications in the use of the means employed.'"[6] One scenario where ANH could become morally optional involves the wasting syndrome called cachexia, where patients continue to lose their body mass despite being provided with adequate nutrition. Here, providing assisted nutrition and hydration actually does not nourish the patient.

New research from two research groups has revealed that cachexia is linked to the transformation of white fat into brown fat[7] and that this transformation is driven in part by a protein called parathyroid hormone-related protein (PTHrP) that is released by tumors.[8] First, white fat normally stores calories while brown fat burns them to generate heat. A team of Spanish scientists has discovered that in mice and patients with cancer-associated cachexia, white fat has been transformed into brown fat, and that this transformation leads to increased energy consumption and organ wasting. Next, American scientists have discovered that PTHrP is one molecule that can covert white fat into brown fat. Blocking the activity of PTHrP not only prevented cancer associated wasting almost completely but also improved muscle function in the treated mice. The report also showed that a significant number of patients with cachexia had elevated levels of PTHrP in their blood. These patients had significantly lower lean body mass and were producing more heat at rest than other cancer patients. This data suggests that giving cachexic patients drugs that block PTHrP activity could increase the effectiveness of ANH and prolong patient lives.

The Biological Basis for Memory and the Power to Control Memory

Two recent papers have continued to reveal the biological basis for memory, opening up the real possibility that we will soon be able to manipulate human memories. First, a collaborative team again from the Salk Institute in La Jolla, California,

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[6] US Conference of Catholic Bishops, *Ethical and Religious Directives for Catholic Health Care Services*, 5th ed. (Washington, DC: USCCB, 2009), n. 58.

[7] Michele Petruzzelli et al., "A Switch from White to Brown Fat Increases Energy Expenditure in Cancer-Associated Cachexia," *Cell Metabolism* 20.3 (September 2, 2014): 433–447.

[8] Serkan Kir et al., "Tumour-Derived PTH-Related Protein Triggers Adipose Tissue Browning and Cancer Cachexia," *Nature* 513.7516 (September 4, 2014): 100–104.

reports that they have been able to obliterate recognition memory in the mouse by simply disabling brain cells called astrocytes.[9] Mutant mice with the disabled astrocytes were unable to distinguish familiar and novel items in their path. This was a surprising discovery since astrocytes were only thought to be supporters of the nerve cells.

In a second paper, researchers were able to reverse the memories of mice by using light-dependent manipulations.[10] Memories are created and stored in different regions of the brain. For example, emotional memories are stored in the amygdala while location memories are stored in the hippocampus. Both regions of the brain are needed for an organism to remember a particular place as a good or a bad place. The scientists at the Massachusetts Institute of Technology were able to identify the nerve cells in the amygdala and the hippocampus when a male mouse learned to fear a particular location because they received electric shocks to their feet there. Using light based genetic therapy called optogenetics, they then reactivated the hippocampal nerve cells in these fear-conditioned mice, now in the presence of a female mouse—a pleasant experience—to reprogram the mouse's memories, and discovered that these mice had ceased to fear the original place where they had been shocked. Though this technology has not been tested with human patients—and it is unclear if this technology could ever be used with people—this paper certainly indicates that the manipulation of memory is not an unrealistic probability.

Nota Bene: Sexual Compulsion, Human Genes, and the Importance of the Human Microbial Population

Finally, I highlight several papers with bioethical implications. First, a University of Cambridge study indicates that pornography and drugs trigger similar brain activity in addicts.[11] The researchers discovered that three regions—the ventral striatum, the dorsal anterior cingulate, and the amygdala—were activated in sexual addicts when they were viewing sexually explicit content. These are the same regions activated in drug addicts when they are shown drug stimuli. Patients with compulsive sexual behavior also showed higher levels of desire towards sexually explicit videos though they did not necessarily rate them higher on scores that measure enjoyment of them. This suggests that sexual addicts are driven to seek pornography because they want it rather than because they necessarily enjoy it. This abnormal process is known as incentive motivation. It is striking that the researchers caution that their results do not necessarily mean that pornography in itself is addictive. I think that every Catholic priest, based on his experience hearing confession, could make a reasonable argument that it is.

[9] Hosuk Sean Lee et al., "Astrocytes Contribute to Gamma Oscillations and Recognition Memory," *PNAS* 111.32 (August 12, 2014): E3343–E3352.

[10] Roger L. Redondo et al., "Bidirectional Switch of the Valence Associated with a Hippocampal Contextual Memory Engram," *Nature* 513.7518 (September 18, 2014): 426–430.

[11] Valerie Voon et al., "Neural Correlates of Sexual Cue Reactivity in Individuals With and Without Compulsive Sexual Behaviours," *PLoS One* 9.7 (July 11, 2014): e102419.

Next, the size of the human genome continues to shrink. A new study by geneticists at the Spanish National Cancer Research Centre (CINO) in Madrid updates the number of human genes to nineteen thousand genes.[12] This number is nearly two thousand genes fewer than the last count, and it is certainly well below initial estimates of one hundred thousand genes. The paper suggests that human complexity comes not from the number of genes—humans now have a similar number of genes to the simple 1 mm worm called *Caenorhabditis elegans*—but from how they are used to generate the organism. As I have noted in this column several times in the past, this suggests that the organization of an organism's molecules—and not the number of molecules—determines the organism's nature. This is an opening for the substantial form to be reintroduced into the philosophy of nature.

Lastly, a surprising paper reveals that a brief, low dose of antibiotics shortly after birth can have long-lasting consequences on the bacteria that live in the guts of mice, and that this change can lead to obesity when the rodents reach middle age.[13] The experiments indicate that the low doses of antibiotics suppress the growth of bacteria that normally grow in the animal's gut allowing other species to flourish. Strikingly, when the bacteria in the guts of penicillin-treated mice were transferred to germ-free mice, the recipient mice gained weight while control animals did not. This suggests that obesity may not depend solely on what and how much one eats but also on the bacteria inhabiting one's gut. It also suggests that one could "treat" intemperance by simply changing the microbial population living in the patient's intestines, using fecal transplants. As one website memorably put it, skinny people's poop could cure obesity. It would be another instance where technology is being used to "treat" vice.

Rev. Nicanor Pier Giorgio Austriaco, OP

[12] Iakes Ezkurdia et al., "Multiple Evidence Strands Suggest That There May Be as Few as 19,000 Human Protein-Coding Genes," *Human Molecular Genetics*, e-pub June 16, 2014, doi: 10.1093/hmg/ddu309.

13 Laura M. Cox et al., "Altering the Intestinal Microbiota during a Critical Developmental Window Has Lasting Metabolic Consequences," *Cell* 158.4 (August 14, 2014): 705–721.