Reprogrammed cells 'remember,' retain characteristics of their cells of origin

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(PhysOrg.com) -- Investigators at the Massachusetts General Hospital (MGH) Center for Regenerative Medicine have confirmed that induced pluripotent stem cells (iPSCs) retain some characteristics of the cells from which they were derived, something that could both assist and impede potential clinical and research uses. In their report that will be published in *Nature Biotechnology* and has received early online release, the researchers also describe finding that these cellular "memories" fade and disappear as cell lines are cultured through successive generations.

"How faithfully iPSCs can be reprogrammed into a truly embryonic state has been a longstanding question, and we have found that the cell of origin does affect the capacity of iPSCs to differentiate in vitro into particular cell types," says Konrad Hochedlinger, PhD, of the MGH Center for Regenerative Medicine who led the research team. "But when cultured iPSCs go through many rounds of cell division, they lose that memory."

A similar study from researchers at Children's Hospital Boston, published simultaneously in the journal Nature, also finds that cellular "memory" affects the differentiation potential of iPSCs. That report compared iPSCs with cells generated by somatic cell nuclear transfer (NT) - the technique used to clone animals - and finds that NT cells are closer to embryonic stem cells than iPSCs. "We still need to study the mechanisms by which nuclear transfer reprograms cells, because that process seems to work more efficiently and faithfully and may teach us how to make better iPS cells," says George Daley, MD, PhD, who led

the Children's study. Both Hochedlinger and Daley are faculty members at the Harvard Stem Cell Institute (HSCI).

Generated from adult cells, iPSCs have many characteristics of embryonic stem cells but are also known to have important differences. Earlier studies found differences in function and gene expression between iPSCs that appeared to echo characteristics of the original adult cells. To discover whether donor cell patterns of gene expression truly persisted, the MGH team studied cells from genetically identical mice originally generated from iPSCs.

They indeed found differences in gene expression between iPSCs generated from different types of cells - skin cells, two type of immune cells, and muscle progenitor cells - from the same animal. Examining iPSCs generated from different animals revealed that differences based on the cell of origin were even greater than differences based on the animal of origin. There were also significant similarities between iPSCs and cells of origin in factors related to the epigenetic control of gene expression. In addition, the potential of iPSCs to differentiate into particular cell types varied, with those originating from either immune cells or muscle precursions being much easier to coax into forming blood progenitors than were iPSCs derived from skin cells.

Long-term culturing of any type of cell requires regularly splitting cultures into smaller populations and transferring them into new dishes or plates, a process called passaging. Because previous studies had suggested that repeated passaging could strengthen iPSC's similarities to embryonic stem cells, the research team investigated whether the process might help erase the cellular memory. Their experiments confirmed that cell-of-origin-based differences - both transcriptional and epigenetic - became less pronounced with subsequent passaging and totally disappeared by the 16th passage.

"Completely reprogramming cells appears to be a gradual process that continues beyond the iPSC stage, which may explain many of the reported differences between iPSCs and embryonic stem cells," says Hochedlinger. "The propensity of early-passage iPSCs to regenerate specific cell types could have clinical advantages, but there also are implications for the use of iPSCs to model diseases, since we'll need to make sure that differences between cells derived from patients and from healthy controls really reflect a disease process and not this cell-of-origin memory."

Hochedlinger is an associate professor of Stem Cell and Regenerative Biology at Harvard University and Harvard Medical School. Lead author of the Nature Biotechnology paper is Jose Polo, PhD, of the MGH Center for Regenerative Medicine and HCSI.

Massachusetts General Hospital, established in 1811, is the original and largest teaching hospital of Harvard Medical School. The MGH conducts the largest hospital-based research program in the United States, with an annual research budget of more than $600 million and major research centers in AIDS, cardiovascular research, cancer, computational and integrative biology, cutaneous biology, human genetics, medical imaging, neurodegenerative disorders, regenerative medicine, systems biology, transplantation biology and photomedicine.

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