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New research refutes claim iPSCs are prone to immune response

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(Medical Xpress)—Researchers in Japan have injected induced pluripotent stem cells (iPSCs) from mice back into genetically identical mice and report that doing so caused no immune reaction. This contradicts the results of an earlier study that showed using the technique could lead to an immune response that destroyed the injected cells. In this new research, the team, as they report in their paper published in the journal *Nature*, injected iPSCs into a mouse embryo, then transplanted tissue from the grown mice into genetically identical mice, with no apparent immunity response.

iPSCs are cells taken from an organism, such as a mouse or human being, that are reprogrammed to mimic embryonic stem cells. The idea is that such cells can be caused to grow into whatever type of cell is desired, leading to cures for such ailments as diabetes or Parkinson's. To find out if it might work, researchers have been taking cells from donors, reprogramming them, and then injecting them back into the same donor, or at least one that is genetically identical, and then watching to see if they grow into the desired tissue. Such work showed early promise but then hit a roadblock when a team from the University of California reported in 2011 that injecting iPSCs back into a mouse caused an immune response which resulted in the destruction of the cells.

In this new research, the team took a different approach. Instead of taking donor tissue, reprogramming its cells and then injecting it right back into the donor, they instead injected iPSCs into mice embryos,

creating chimeras (organisms with more than one set of genetic information). After the chimera grew to become an adult they took skin and bone marrow samples and transplanted them back into the original donor. Doing so, they report, resulted in no more of an immune response than is typical of stem cell injections.

The team argues that the earlier work by the team at UofC was faulty because they were testing on a different outcome. In that research, the team was looking to create teratomas, a type of tumor, as a proof of concept. The injected iPSCs were rejected and the experiments failed leading to concerns about the viability of using iPSCs as a means of growing new tissue to treat a variety of ailments in humans.

This new research doesn't settle the argument of course, as two different methodologies were used, but it does give researchers hope once again that iPSCs might one day be used to create new tissue, curing people of a wide variety of ailments.

More information: Negligible immunogenicity of terminally differentiated cells derived from induced pluripotent or embryonic stem cells, *Nature* (2013) doi:10.1038/nature11807

Abstract
The advantages of using induced pluripotent stem cells (iPSCs) instead of embryonic stem (ES) cells in regenerative medicine centre around circumventing concerns about the ethics of using ES cells and the likelihood of immune rejection of ES-cell-derived tissues. However, partial reprogramming and genetic instabilities in iPSCs could elicit immune responses in transplant recipients even when iPSC-derived differentiated cells are transplanted. iPSCs are first differentiated into specific types of cells in vitro for subsequent transplantation. Although model transplantation experiments have been conducted using various iPSC-derived differentiated tissues and immune rejections have not been

observed, careful investigation of the immunogenicity of iPSC-derived tissue is becoming increasingly critical, especially as this has not been the focus of most studies done so far. A recent study reported immunogenicity of iPSC- but not ES-cell-derived teratomas and implicated several causative genes. Nevertheless, some controversy has arisen regarding these findings. Here we examine the immunogenicity of differentiated skin and bone marrow tissues derived from mouse iPSCs. To ensure optimal comparison of iPSCs and ES cells, we established ten integration-free iPSC and seven ES-cell lines using an inbred mouse strain, C57BL/6. We observed no differences in the rate of success of transplantation when skin and bone marrow cells derived from iPSCs were compared with ES-cell-derived tissues. Moreover, we observed limited or no immune responses, including T-cell infiltration, for tissues derived from either iPSCs or ES cells, and no increase in the expression of the immunogenicity-causing Zg16 and Hormad1 genes in regressing skin and teratoma tissues. Our findings suggest limited immunogenicity of transplanted cells differentiated from iPSCs and ES cells.