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SCNT-Derived ESCs with Mismatched Mitochondria Trigger an Immune Response in Allogeneic Hosts

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Abstract: The generation of pluripotent stem cells by somatic cell nuclear transfer (SCNT) has recently been achieved in human cells and sparked new interest in this technology. The authors reporting this methodical breakthrough speculated that SCNT would allow the creation of patient-matched embryonic stem cells, even in patients with hereditary mitochondrial diseases. However, herein we show that mismatched mitochondria in nuclear-transfer-derived embryonic stem cells (NT-ESCs) possess alloantigenicity and are subject to immune rejection. In a murine transplantation setup, we demonstrate that allogeneic mitochondria in NT-ESCs, which are nucleus-identical to the recipient, may trigger an adaptive alloimmune response that impairs the survival of NT-ESC grafts. The immune response is adaptive, directed against mitochondrial content, and amenable for tolerance induction. Mitochondrial alloantigenicity should therefore be considered when developing therapeutic SCNT-based strategies.

Statement: *Stem cell therapies hold vast potential for repairing organs and treating disease. The greatest hope rest on the potential of pluripotent stem cells, which can become nearly any kind of cell in the body. One method for obtaining pluripotent stem cells, called somatic cell nuclear transplantation (SCNT), involves taking the nucleus of an adult cell and injecting it into an egg cell from which the nucleus has been removed. The promise of SCNT is that the nucleus of a patient's skin cell, for example, could be usedto create pluripotent cells that might be able to repair a part of that patient's body. Oneattraction of SCNT has always been that the genetic identity of the new pluripotent cell would be the same as the patient's, since the transplanted nucleus carries the patient's DNA. The hope has been that this would eliminate the problem of the patient's immune system attacking the pluripotent cells as foreign tissue, which is a problem with most organs and tissues when they are transplanted from one patient to another. Schrepfer and her colleagues used cells that were created by transferring the nuclei of adult mouse cells into enucleated eggs cells from genetically different mice. When transplanted back into the nucleus donor strain, the cells were rejected although there were only two single nucleotide substitutions in the mitochondrial DNA (mtDNA) of these SCNT-derived cells compared to the mtDNA of the nucleus donor. We were surprised to find that just two small differences in mtDNA was enough to cause an immune reaction. Until recently, researchers were able to perform SCNT in many species, but not in humans. When scientists announced success in performing SCNT with human cells last year, it reignited interest in eventually using the technique for human therapies. Although most interest in the stem cell research community is focused on a different kind of pluripotent stem cell called an "induced pluripotent stem cell," there may be some applications for which SCNT-derived pluripotent cells are better suited. The recently discovered immunological reactions will be a consideration if clinicians ever use SCNT-derived stem cells in human therapy, but it should not block such use. The Altmetric score (published by Cell Stem Cell) of 42 puts the article in the top 5% of all articles ranked by attention (= 96th percentile compared to articles of the same age).*

Background:
The manuscript represents interdisciplinary work of 10 UKE scientistsand clinicians (TSI-Lab, Cardiovascular Surgery, and Bioinformatics Service Facility at the University Medical Center Hamburg- Eppendorf). First and last authors are UKE scientists (see above). Schrepfer is

heading the Transplant and Stem Cell Immunobiology (TSI)-lab at the University Heart Center in Hamburg, Germany, and at the German Center for Cardiovascular Research in Hamburg as well as Visiting Professor at Stanford University (CT Surgery and Cardiovascular Institute). Stanford researcher Irving Weissman and Robert Robbins were also involved in this research. Investigators taking part included those from the University Heart Center in Hamburg, Germany, the Cardiovascular Research Center Hamburg and the German Center for Cardiovascular Research, as well from Newcastle University in Newcastle, United Kingdom.