Techniques to eliminate mitochondrial diseases are honed in a new study that outlines a path to preventing the transmission of damaged mitochondria from a mother to her offspring [1]. These promising findings in Nature come on the heels of a similar study published in the same journal online in October 2012 [2, 3].

Mitochondria and, consequently, mitochondrial diseases are transmitted by the mother to offspring through the oocyte. Daniel Paull et al. circumvented this scheme of nature by transplanting the nuclear DNA from one human oocyte into the cytoplasm of an oocyte from which a nucleus had been removed. To test whether the procedure worked, the authors parthenogenetically activated the newly derived oocytes.

The resulting embryos developed efficiently and took on the mitochondria of the host oocytes. Of the 18 oocytes, 7 made it to the blastocyst stage. The researchers generated three pluripotent stem cell lines from these blastocysts and passaged the cells for more than a year. Mitochondrial DNA transferred with the nuclear genome was initially present at low levels—below 1 percent—but waned to undetectable levels in the stem cell lines and in differentiated cells created from these lines. The mitochondria also were functional, for instance yielding oxygen consumption rates indistinguishable from controls.

Such extreme manipulation of an oocyte raises concerns about introducing epigenetic alterations. To address this concern, the researchers examined gene expression in cell lines derived from manipulated embryos and found it to be comparable to that seen in control cell lines derived from unmanipulated embryos.

The findings jibe with a study published online last October by Masahito Tachibana et al. [2], which employed a similar technique. Both techniques result in the replacement of donor mitochondria in resulting embryos and found it to be comparable to that seen in control cell lines derived from unmanipulated embryos.

The new study places insulin/IGF signaling as one of the earliest programs to the gonad and adrenal cortex in mice, according to a new report.

The mammalian gonads and adrenal cortex develop from a common structure in the early embryo, the adreno-genital primordium (AGP). The AGP then produces the gonadal primordium, which has the potential to differentiate into either testes or ovaries. Proper gonadal differentiation requires steroidogenic factor 1 (SF1, a.k.a. NR5A1), a nuclear receptor expressed in the AGP and gonadal primordium. SF1 operates with the Y chromosome-encoded protein SRY to promote differentiation of the testis. In the absence of SRY activity, the ovarian differentiation program dominates.

A previous study by Serge Nef and colleagues showed that signaling through insulin/IGF is required for testis determination, but it was unclear whether insulin/IGF had its impact on cell fate decisions at the stage of testis determination or earlier during the period of formation of the AGP.

The new findings show that insulin/IGF signaling affects the development of the AGP and likely the gonadal primordium as well. The researchers examined mice mutant for both the IGF type I receptor (Igf1r) and the insulin receptor (Insr). The mice failed to develop an adrenal cortex and also showed complete embryonic XY gonadal sex reversal caused by a delay of Sry upregulation and subsequent failure of the testicular genetic program. Both XY and XX mice ultimately developed ovaries.

The double-mutant mice had a reduced number of SF1-expressing cells and the cells that expressed SF1 did so at reduced levels, a finding that may explain the dysregulation of Sry. The gene-expression program in the somatic progenitor cells to the gonad was also affected in the knockout mice. Previous studies have suggested that these progenitors express a battery of genes that are found in both gonads before committing to the male or female fate. The new study showed a similar pattern and provided compelling evidence that this program was disrupted in the double mutant.

The new study places insulin/IGF signaling as one of the earliest known events in the differentiation of the gonads and adrenal cortex, a finding in line with previous work showing that insulin/IGF can regulate cell proliferation, differentiation, metabolism, and cell survival in numerous physiological contexts.


Insulin/IGF Signaling Goads Gonads, Adrenal Glands
BOR–Papers in Press published 9 January 2013
DOI: 10.1095/biolreprod.113.107854

Signaling through insulin/insulin-like growth factor (IGF) guides the development of the cells that give rise to the gonad and adrenal cortex in mice, according to a new report.

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Immune Imbalance Leads to Abortion
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DOI: 10.1095/biolreprod.113.108035

Two new studies show how dysregulation of the immune system in the uterus can lead to spontaneous abortion.

Techniques to eliminate mitochondrial diseases are honed in a new study that outlines a path to preventing the transmission of damaged mitochondria from a mother to her offspring [1]. These promising findings in Nature come on the heels of a similar study published in the same journal online in October 2012 [2, 3].

Mitochondria and, consequently, mitochondrial diseases are transmitted by the mother to offspring through the oocyte. Daniel Paull et al. circumvented this scheme of nature by transplanting the nuclear DNA from one human oocyte into the cytoplasm of an oocyte from which a nucleus had been removed. To test whether the procedure worked, the authors parthenogenetically activated the newly derived oocytes.

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Such extreme manipulation of an oocyte raises concerns about introducing epigenetic alterations. To address this concern, the researchers examined gene expression in cell lines derived from manipulated embryos and found it to be comparable to that seen in control cell lines derived from unmanipulated embryos.

The findings jibe with a study published online last October by Masahito Tachibana et al. [2], which employed a similar technique. Both techniques result in the replacement of donor mitochondria in resulting stems cells; however, in the study by Tachibana and colleagues, about half of the manipulated zygotes had an extra pronucleus, which may indicate an abnormal chromosome number. In the earlier study, researchers transferred spindle-chromosome complexes to host oocytes; in the new study, researchers were able to successfully transfer the nuclear DNA with an incompletely assembled spindle by cooling the nucleus, either by cryopreservation or by keeping it at room temperature, which resulted in reversible, partial depolymerization of the spindle.

References