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Mutated mitochondria could hold back stem-cell therapies

Stem cells derived from older people may need to be screened before use in therapies.

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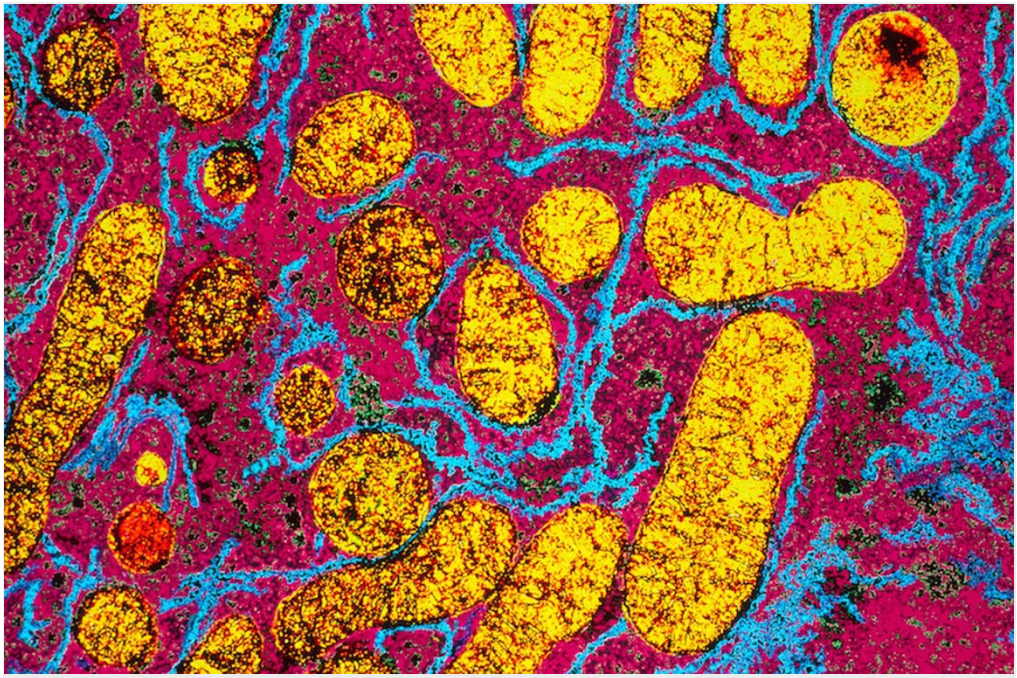

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Mitochondria (shown in yellow) provide energy to cells.

Induced pluripotent stem cells (iPS) — those derived from adult cells — are inching closer to the clinic. But as a new study helps to show, much work remains before the field can yield mainline treatments.

The older a patient is, the more likely it is that induced pluripotent stem (iPS) cells derived from them will carry genetic mutations that could affect the cells' function, researchers report in *Cell Stem Cell*[1]. These mutations are found in the DNA of mitochondria, organelles that power the cell and have their own genomes. Each cell can contain hundreds of mitochondria.

To test how genetic variations in mitochondria might affect iPS cells, a team led by reproductive biologist Shoukhrat Mitalipov at Oregon Health and Science University in Portland collected skin and blood samples from a 72-year-old volunteer. The scientists sequenced DNA from the samples, then transformed the adult cells into stem cells by infecting them with viruses that cause the expression of several genes involved in early embryonic development.

When the researchers isolated and sequenced DNA from the resulting stem cells, they did not find a high rate of mutations in the mitochondria overall. But when they examined DNA from individual cells chosen at random, they found a wide variety of mutations in mitochondria that had been obscured in the larger pool of cells.

Cracking the code

Next, the researchers analysed skin and blood samples from 14 people aged between 24 and 72. The older the person was, the more mutations his or her mitochondria acquired. A few of the mutations occurred in DNA that coded for proteins — which might affect how well the iPS cells would function if transplanted into a patient.

"It's one of those things most of us don't think about," says Jeanne Loring, a stem-cell biologist at the Scripps Research Institute in La Jolla, California. Her lab is working towards using iPS cells to treat Parkinson's disease, and Loring now plans to go back and examine the mitochondria in her cell lines. She suspects that it will be fairly easy for researchers to screen cells for use in therapies.

Mitalipov suggests that researchers who want to use iPS cells in treatments should isolate at least ten cells, and then use the one with the best mitochondria to create a cell line.

He also says that the findings support the use of a technique called somatic-cell nuclear transfer, in which embryonic stem cells are created by transferring the nucleus of a patient's cell into a healthy young egg cell stripped of its own nucleus. This altered donor cell is then used to generate a blastocyst, or early-stage human embryo, that contains mitochondria from the healthy donor and nuclear DNA from the patient.

But Loring says that this technique is much more difficult than creating iPS cells, and only a few labs — including Mitalipov's — have the skill to do it.

Subtle variations

Dieter Egli, a regenerative-medicine researcher at the New York Stem Cell Foundation, says that the findings provide an argument for using embryonic stem cells instead of iPS cells. "This is definitely going to have an impact" on iPS trials, he says. Screening cell lines is especially important if researchers are to use them in the clinic rather than just in the lab. "For therapy, you can't just assume it does or doesn't work," he says.

Mitalipov says that many researchers are moving away from the idea of using a person's own cells for every treatment, and towards creating banks of iPS cells derived from a variety of people; patients could receive a transplant from the donor whose cells most closely match their own. The Japanese trial was halted after a recipient's cells acquired mutations during the iPS process, and the researchers have applied for permission to treat future trial participants with cells from such a bank.

But Egli adds that researchers will also have to determine how meaningful the mitochondrial mutations are, because many biological factors could present problems. Researchers studying how iPS cells differ from embryonic stem cells have found that the two cell types can have differences in chemical markers on their DNA that affect how genes can be expressed[2], for instance. "It's going to be very hard to find a cell line that's perfect," he says.

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References

1. Kang, E., *et al. Cell Stem Cell* http://dx.doi.org/10.1016/j.stem.2016.02.005 (2016).
2. Ma, H., *et al. Nature* **511**, 177–183 (2014).