Study shows aging process increases DNA mutations in important type of stem cell

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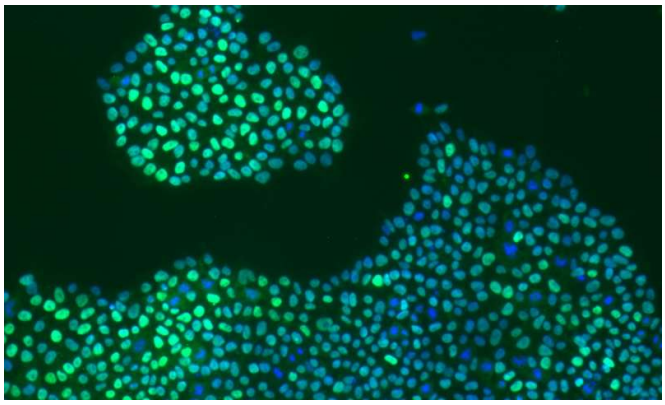

Induced pluripotent stem cells produced for the study and viewed under a microscope. Credit: Scripps Translational Science Institute

As it is in much of life, the aging process isn't kind to an important type of stem cell that has great therapeutic promise.

Researchers at the Scripps Translational Science Institute (STSI) and The Scripps Research Institute (TSRI) who looked at the effect of aging on induced pluripotent stem cells (iPSCs) found that genetic mutations increased with the age of the donor who provided the source cells, according to study results published today by the journal *Nature Biotechnology*.

The findings reinforce the importance of screening iPSCs for potentially harmful DNA mutations before using them for therapeutic purposes, said lead investigators Ali Torkamani, Ph.D., director of genome informatics at STSI, and Kristin Baldwin Ph.D., the study's co-lead investigators and associate professor of molecular and cellular neuroscience at the Dorris Neuroscience Center at TSRI.

"Any time a cell divides, there is a risk of a mutation occurring. Over time, those risks multiply," Torkamani said. "Our study highlights that increased risk of mutations in iPSCs made from older donors of source cells."

Researchers found that iPSCs made from donors in their late 80s had twice as many mutations among protein-encoding genes as stem cells made from donors in their early 20s.

That trend followed a predictable linear track paired with age with one exception. Unexpectedly, iPSCs made from blood cells donated by people over 90 years old actually contained fewer mutations than what researchers had expected. In fact, stem cells from those extremely elderly participants had mutation numbers more comparable to iPSCs made from donors one-half to two-thirds younger.

Researchers said the reason for this could be tied to the fact that blood stem cells remaining in elderly people have been protected from mutations over their lifetime by dividing less frequently.

"Using iPSCs for treatment has already been initiated in Japan in a woman with age-related macular degeneration," said paper co-author and STSI Director Eric Topol, M.D. "Accordingly, it's vital that we fully understand the effects of aging on these cells being cultivated to treat patients in the future."

STSI is a National Institutes of Health-sponsored site led by Scripps Health in collaboration with TSRI. This innovative research partnership is leading the effort to translate wireless and genetic medical technologies into high-quality, cost-effective treatments and diagnostics for patients.

Of the 336 different mutations that were identified in the iPSCs generated for the study, 24 were in genes that could impair cell function or trigger tumor growth if they malfunctioned.

How troublesome these mutations could be depends on how well the stem cells are screened to filter out the defects and how they are used therapeutically, Torkamani said. For example, cells made from iPSCs for a bone marrow transplant would be potentially dangerous if they contained a TET2 gene mutation linked to blood cancer, which surfaced during the study.

"We didn't find any overt evidence that these mutations automatically would be harmful or pathogenic," he said.

For the study, researchers tapped three sources for 16 participant blood samples: The Wellderly Study, an ongoing STSI research project that is searching for the genetic secrets behind lifelong health by looking at the genes of healthy elderly people ages 80 to 105; the STSI GeneHeart Study, which involves people with coronary artery disease; and TSRI's research blood donor program.

The iPSCs were generated by study co-authors Valentina Lo Sardo, Ph.D., and Will Ferguson, M.S., researchers in the TSRI group led by Baldwin.

"When we proposed this study, we weren't sure whether it would even be possible to grow iPSCs from the blood of the participants in the Wellderly Study, since others have reported difficulty in making these stem cells from aged patients," Baldwin said. "But through the hard work and careful experiments designed by Valentina and Will, our laboratories became the first to produce iPSCs from the blood of extremely elderly people."

More information: Influence of donor age on induced pluripotent stem cells, *Nature Biotechnology*, nature.com/articles/doi:10.1038/nbt.3749

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