

New measurements reveal differences between stem cells for treating retinal degeneration

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By growing two types of stem cells in a "3-D culture" and measuring their ability to produce retinal cells, a team lead by St. Jude Children's Research Hospital researchers has found one cell type to be better at producing retinal cells.

The research not only reveals which stem cell type might be better for treating retinal degeneration, but it also demonstrates a standardized method for quantifying the effectiveness of different stem cells for such therapies.

The research was led by Michael Dyer, Ph.D., a member of the St. Jude Department of Developmental Neurobiology and a Howard Hughes Medical Institute investigator. The findings were published in the July 2 edition of the journal *Cell Stem Cell*.

Stem cells are immature cells that can differentiate into more specialized cells in the body. In early clinical trials, researchers are testing whether stem cells can be differentiated into cells to replace those that are defective and die off in diseases such as age-related macular degeneration, retinitis pigmentosa and Stargardt's disease. Such degeneration is the leading cause of vision loss, affecting more than 10 million people in the U.S.—more than cataracts and glaucoma combined.

While such clinical trials have shown early promise, there are many scientific questions to be answered. "One important question is whether it makes a difference where the stem cells come from," Dyer said. "Our research sought to explore that question and also to learn more about the biology of these stem cells."

The researchers compared two types of stem cells called "induced pluripotent stem cells," which can be generated from adult cells. The stem cells they compared were fibroblast-derived cells generated from skin, and those generated from mature eye cells called rod photoreceptor cells.

Scientists previously thought that induced [pluripotent stem cells](#) could not be made from adult neurons without introducing a mutation that switches off a key regulatory gene called p53. Dyer's lab developed a new method for making stem cells from neurons that did not require p53 inactivation. This 3-D culture technique involved surrounding the neurons undergoing reprogramming with normal retinal neurons, to create a more natural environment for producing stem cells from neurons. This technique contrasts with the more common culture technique of growing the cells in layers on culture dishes, which is not successful for such cells. Once the stem cells are produced, they can then be used to make retinal cells in 3-D cultures.

Besides the 3-D culture technique, the researchers also used a set of measurements, called STEM-RET, which enabled them to quantify precisely how successful different retinal cells are in generating retinal cells. Their STEM-RET analysis revealed that the rod-derived stem cells produced more retinal cells than did the fibroblast stem cells. The fibroblast-derived retinal cells were missing some [cell types](#) needed for fully functional retinas.

Dyer and his colleagues also explored the biological differences in the

two stem cell types that could explain their differences in producing retinal cells. Specifically, the researchers analyzed differences in the epigenetic control machinery of the two types. Such epigenetic machinery of cells consists of biological switches that control the cell's genes. These are distinct from the genetic control machinery built into the DNA structure of the cell's genes themselves.

Scientists believe that different stem cell types may retain an "epigenetic memory"—a distinctive set of epigenetic switches, even as they are reprogrammed from mature cell types. This "memory" affects how well the stem cells produce different cell types.

In their analysis of the retinal cells, the researchers detected a type of epigenetic switch, called CTCF, which contributes to the epigenetic memory of the rod-derived stem cells. This epigenetic switch, they believe, could play a role in making the rod stem cells a superior source of retinal cells.

Dyer said that STEM-RET scoring of stem cells represents a significant advance in determining which stem cells to use in retinal stem cell therapies. "There has long been a debate in the field about how to standardize the quantification of stem cell differentiation," he said. "Our STEM-RET method enables that standardization, which means that laboratories can accurately compare their results with one another and different stem cell lines can be compared with one another. We believe the method could be adopted widely."

Epigenetic analysis of such stem cells could lead to "epigenetic fingerprints" characterizing different stem cell types. "Such fingerprints would tell researchers which stem cell lines would most likely be effective in making [retinal cells](#), bone marrow cells or other types of mature cells for therapeutic purposes," Dyer said.

The 3-D culture technique and STEM-RET measurement protocol allow scientists to manipulate [stem cells](#) genetically and with drugs to discover ways to better reprogram the cells into functional mature cells for therapeutic use.

Provided by St. Jude Children's Research Hospital

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