Scientists find potential new use for cancer drug in gene therapy for blood disorders

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Bruce Torbett, PhD, is an associate professor at The Scripps Research Institute. Credit: Photo courtesy of The Scripps Research Institute.

Scientists working to make gene therapy a reality have solved a major

hurdle: how to bypass a blood stem cell's natural defenses and efficiently insert disease-fighting genes into the cell's genome.

In a new study led by Associate Professor Bruce Torbett at The Scripps Research Institute (TSRI), a team of researchers report that the drug rapamycin, which is commonly used to slow cancer growth and prevent organ rejection, enables delivery of a therapeutic dose of genes to blood stem cells while preserving stem cell function.

These findings, published recently online ahead of print by the journal *Blood*, could lead to more effective and affordable long-term treatments for blood cell disorders in which mutations in the DNA cause abnormal cell functions, such as in leukemia and sickle cell anemia.

Improving Gene Delivery to Blood Stem Cells

Viruses infect the body by inserting their own genetic material into human cells. In gene therapy, however, scientists have developed "gutted" viruses, such as the human immunodeficiency virus (HIV), to produce what are called "viral vectors." Viral vectors carry therapeutic genes into cells without causing viral disease. Torbett and other scientists have shown that HIV vectors can deliver genes to blood stem cells.

For a disease such as leukemia or leukodystrophy, where mutations in the DNA cause abnormal cell function, efficiently targeting the stem cells that produce these blood cells could be a successful approach to halting the disease and prompting the body to produce healthy blood cells.

"If you produce a genetic modification in your blood stem cells when you are five years old, these changes are lifelong," said Torbett. Furthermore, the gene-modified stem cells can develop into many types of cells that travel throughout the body to provide therapeutic effects.

However, because cells have adapted defense mechanisms to overcome disease-causing viruses, engineered viral vectors can be prevented from efficiently delivering genes. Torbett said that when scientists extract blood stem cells from the body for gene therapy, HIV viral vectors are usually able to deliver genes to only 30 to 40 percent of them. For leukemia, leukodystrophy or genetic diseases where treatment requires a reasonable number of healthy cells coming from stem cells, this number may be too low for therapeutic purposes.

This limitation prompted Torbett and his team, including TSRI graduate student Cathy Wang, the first author of the study, to test whether rapamycin could improve delivery of a gene to blood stem cells. Rapamycin was selected for evaluation based on its ability to control virus entry and slow cell growth.

The researchers began by isolating stem cells from cord blood samples. They exposed the blood stem cells to rapamycin and HIV vectors engineered to deliver a gene for a green florescent protein, which causes cells to glow. This fluorescence provided a visual marker that helped the researchers track gene delivery.

The researchers saw a big difference in both mouse and human stem cells treated with rapamycin, where therapeutic genes were inserted into up to 80 percent of cells. This property had never been connected to rapamycin before.

Helping Blood Stem Cells Survive

The researchers also found that rapamycin can keep stem cells from differentiating as quickly when taken out of the body for gene therapy. This is important because scientists need time to work on extracted blood stem cells—yet once these cells leave the body, they begin to differentiate if manipulated into other types of blood cells and lose the

ability to remain as stem cells and pass on therapeutic genes.

"We wanted to make sure the conditions we will use preserve stem cells, so if we transplant them back into our animal models, they act just like the original stem cells," said Torbett. "We showed that in two sets of animal models, stem cells remain and produce gene-modified cells."

The researchers hope these methods could someday be useful in the clinic. "Our methods could reduce costs and the amount of preparation that goes into modifying blood stem cells using viral vector gene therapy," said Wang. "It would make gene therapy accessible to a lot more patients."

She said the next steps are to carry out preclinical studies using rapamycin with stem cells in other animal models and then see if the method is safe and effective in humans. The team is also working to delineate the dual pathways of rapamycin's method of action in blood stem cells.

More information: The study can be accessed at bloodjournal.hematologylibrary … blood-2013-12-546218

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