New gene repair technique promises advances in regenerative medicine

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Using human pluripotent stem cells and DNA-cutting protein from meningitis bacteria, researchers from the Morgridge Institute for Research and Northwestern University have created an efficient way to target and repair defective genes.

Writing today (Monday, Aug. 12, 2013) in the *Proceedings of the National Academy of Sciences*, the team reports that the novel technique is much simpler than previous methods and establishes the groundwork for major advances in regenerative medicine, drug screening and biomedical research.

Zhonggang Hou of the Morgridge Institute's regenerative biology team and Yan Zhang of Northwestern University served as first authors on the study; Dr. James Thomson, director of regenerative biology at the Morgridge Institute, and Erik Sontheimer, professor of molecular biosciences at Northwestern University, served as principal investigators.

"With this system, there is the potential to repair any genetic defect, including those responsible for some forms of breast cancer, Parkinson's and other diseases," Hou said. "The fact that it can be applied to human pluripotent stem cells opens the door for meaningful therapeutic applications."

Zhang said the Northwestern University team focused on *Neisseria meningitidis* bacteria because it is a good source of the Cas9 protein needed for precisely cleaving damaged sections of DNA.

"We are able to guide this protein with different types of small RNA molecules, allowing us to carefully remove, replace or correct problem genes," Zhang said. "This represents a step forward from other recent technologies built upon proteins such as zinc finger nucleases and TALENs."

These previous gene correction methods required engineered proteins to help with the cutting. Hou said scientists can synthesize RNA for the new process in as little as one to three days – compared with the weeks or months needed to engineer suitable proteins.

Thomson, who also serves as the James Kress Professor of Embryonic Stem Cell Biology at the University of Wisconsin–Madison, a John D. MacArthur professor at UW–Madison's School of Medicine and Public Health and a professor in the department of molecular, cellular and developmental biology at the University of California, Santa Barbara, says the discovery holds many practical applications.

"Human pluripotent stem cells can proliferate indefinitely and they give rise to virtually all human cell types, making them invaluable for regenerative medicine, drug screening and biomedical research," Thomson says. "Our collaboration with the Northwestern team has taken us further toward realizing the full potential of these cells because we can now manipulate their genomes in a precise, efficient manner."

Sontheimer, who serves as the Soretta and Henry Shapiro Research Professor of Molecular Biology with Northwestern's department of molecular biosciences, Center for Genetic Medicine and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, says the team's results also offer hopeful signs about the safety of the technique.

"A major concern with previous methods involved inadvertent or off-target cleaving, raising issues about the potential impact in regenerative medicine applications," he said. "Beyond overcoming the safety obstacles, the system's ease of use will make what was once considered a difficult project into a routine laboratory technique, catalyzing future research."

More information: Efficient genome engineering in human pluripotent stem cells using Cas9 from Neisseria meningitidis , www.pnas.org/cgi/doi/10.1073/pnas.1313587110

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