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Mechanistic insight into immortal cells could speed clinical use

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The mechanistic understanding of the relatively new technique for growing cells in culture indefinitely - known as conditional reprogramming - has been deciphered and reported in the February 25th issue of *PLOS ONE*. Researchers at Georgetown Lombardi Comprehensive Cancer Center say identifying the mechanisms of immortalization lays the groundwork for future clinical use of these cells.

Investigators discovered the signaling pathways associated with the two primary components of the "conditional reprogramming" technique developed at Georgetown University—feeder cells derived from mouse fibroblasts and a Rho kinase inhibitor—work in parallel to immortalize the cells. Both the inhibitor and feeder cells suppress terminal differentiation of cells allowing them to keep multiplying. The feeder cells achieve this by secreting a specific set of proteins.

"A lot more work remains before we can provide a complete formulation, which can replace the feeder cells utilized by researchers to generate patient-specific cells for gene correction or regenerative therapies," says the study's senior investigator, Geeta Upadhyay, PhD, research assistant professor of oncology at Georgetown Lombardi.

The ability to generate conditionally reprogrammed cells, which was first described in 2012 in the *American Journal of Pathology* by Richard Schlegel, MD, PhD, of Georgetown Lombardi, and colleagues, holds the promise of significantly advancing personalized medicine, Upadhyay

says. The method can keep both normal and diseased cells alive indefinitely—which previously had not been possible. When the two components are withdrawn, normal cells begin to differentiate.

Schlegel published a demonstration of the technique's power in 2012 in the *New England Journal of Medicine*, when the method was used to grow cells in the lab from a man with a lung tumor that contained HPV and for which there was no known therapy. Using both normal and tumor cells from the patient, the investigators screened several drugs and identified a therapy which was effective clinically.

Upadhyay has identified the precise cell pathways that the two key components used to immortalize cells, and also found that the feeder cells secrete 14 different proteins to do their work. Both discoveries will likely speed clinical application, she says, because mouse feeder cells would not be needed if the 14 proteins they secrete could be used in isolated and purified form.

"There has been much global interest in conditionally reprogrammed cells, but not all laboratories have the capacity to irradiate the feeder cells, which pushes them to secrete the factors. With a cocktail of purified proteins, we can reduce the possibility of contamination of human cells by mouse feeder cells."

Provided by Georgetown University Medical Center