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1 gene lost = 1 limb regained? Scientists demonstrate mammalian regeneration through single gene deletion

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A quest that began over a decade ago with a chance observation has reached a milestone: the identification of a gene that may regulate regeneration in mammals. The absence of this single gene, called p21, confers a healing potential in mice long thought to have been lost through evolution and reserved for creatures like flatworms, sponges, and some species of salamander. In a report published today in the *Proceedings of the National Academy of Sciences*, researchers from The Wistar Institute demonstrate that mice that lack the p21 gene gain the ability to regenerate lost or damaged tissue.

Unlike typical mammals, which heal wounds by forming a scar, these mice begin by forming a blastema, a structure associated with rapid cell growth and de-differentiation as seen in amphibians. According to the Wistar researchers, the loss of p21 causes the cells of these mice to behave more like embryonic stem cells than adult mammalian cells, and their findings provide solid evidence to link tissue regeneration to the control of cell division.

"Much like a newt that has lost a limb, these mice will replace missing or damaged tissue with healthy tissue that lacks any sign of scarring," said the project's lead scientist Ellen Heber-Katz, Ph.D., a professor in Wistar's Molecular and Cellular Oncogenesis program. "While we are just beginning to understand the repercussions of these findings, perhaps, one day we'll be able to accelerate healing in humans by

temporarily inactivating the p21 gene."

Heber-Katz and her colleagues used a p21 knockout mouse to help solve a mystery first encountered in 1996 regarding another mouse strain in her laboratory. MRL mice, which were being tested in an autoimmunity experiment, had holes pierced in their ears to create a commonly used life-long identification marker. A few weeks later, investigators discovered that the earholes had closed without a trace. While the experiment was ruined, it left the researchers with a new question: Was the MRL mouse a window into mammalian regeneration?

The discovery set the Heber-Katz laboratory off on two parallel paths. Working with geneticists Elizabeth Blankenhorn, Ph.D., at Drexel University, and James Cheverud, Ph.D., at Washington University, the laboratory focused on mapping the critical genes that turn MRL mice into healers. Meanwhile, cellular studies ongoing at Wistar revealed that MRL cells behaved very differently than cells from "non-healer" mouse strains in culture. Khamilia Bedebaeva, M.D., Ph.D., having studied genetic effects following the Chernobyl reactor radiation accident, noticed immediately that these cells were atypical, showing profound differences in cell cycle characteristics and DNA damage. This led Andrew Snyder, Ph.D., to explore the DNA damage pathway and its effects on cell cycle control.

Snyder found that p21, a cell cycle regulator, was consistently inactive in cells from the MRL mouse ear. P21 expression is tightly controlled by the tumor suppressor p53, another regulator of cell division and a known factor in many forms of cancer. The ultimate experiment was to show that a mouse lacking p21 would demonstrate a regenerative response similar to that seen in the MRL mouse. And this indeed was the case. As it turned out, p21 knockout mice had already been created, were readily available, and widely used in many studies. What had not been noted was that these mice could heal their ears.

"In normal cells, p21 acts like a brake to block cell cycle progression in the event of DNA damage, preventing the cells from dividing and potentially becoming cancerous," Heber-Katz said. "In these mice without p21, we do see the expected increase in DNA damage, but surprisingly no increase in cancer has been reported."

In fact, the researchers saw an increase in apoptosis in MRL mice - also known as programmed cell death - the cell's self-destruct mechanism that is often switched on when DNA has been damaged. According to Heber-Katz, this is exactly the sort of behavior seen in naturally regenerative creatures.

"The combined effects of an increase in highly regenerative cells and apoptosis may allow the cells of these organisms to divide rapidly without going out of control and becoming cancerous," Heber-Katz said. "In fact, it is similar to what is seen in mammalian embryos, where p21 also happens to be inactive after DNA damage. The down regulation of p21 promotes the induced pluripotent state in mammalian cells, highlighting a correlation between stem cells, tissue regeneration, and the cell cycle."

Provided by The Wistar Institute