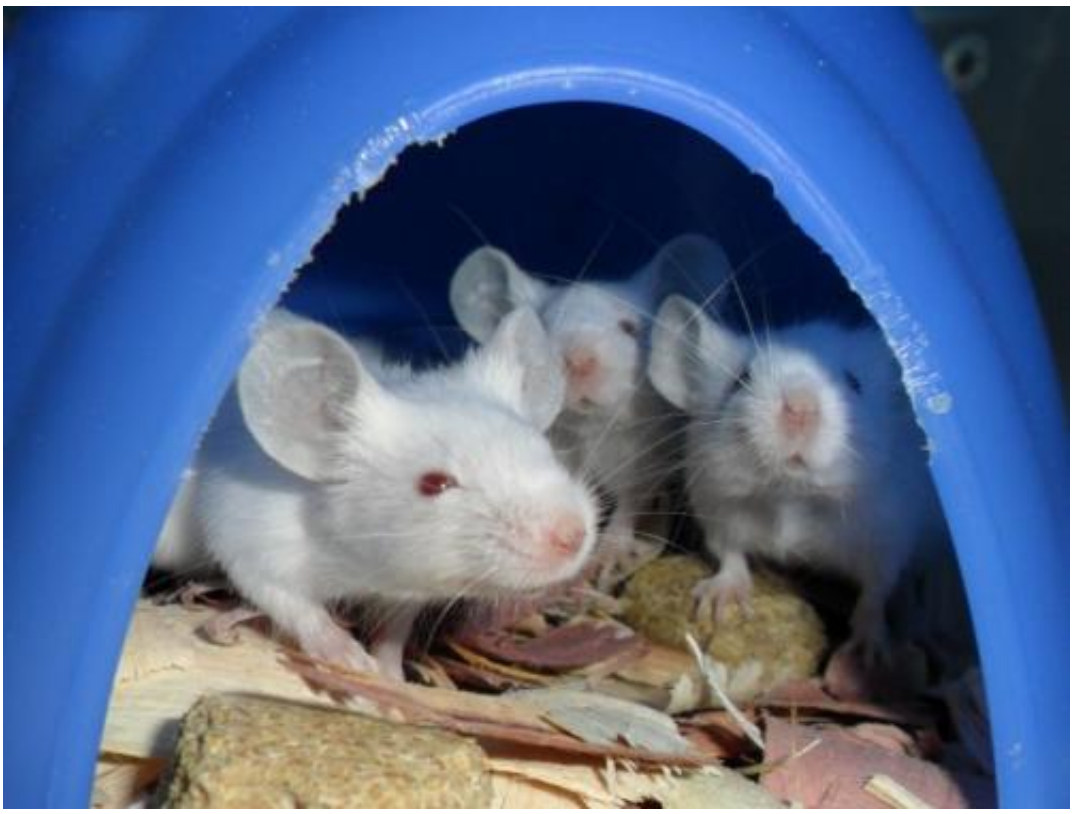
Medical Xpress

Study demonstrates drug-induced ear tissue regeneration in mice

June 3 2015



Credit: Martha Sexton/public domain

A study led by Ellen Heber-Katz, PhD, of the Lankenau Institute for Medical Research (LIMR), part of Main Line Health (MLH), shows that a primordial form of energy production that still exists in mammals can be harnessed to achieve spontaneous tissue regeneration in mice, without the need for added stem cells. The study findings were reported in the

June 3, 2015, issue of *Science Translational Medicine*, a peer-reviewed journal of the American Association for the Advancement of Science. Key collaborators in the study, which was supported by grants from the National Institutes of Health, included Yong Zhang, PhD (LIMR), Iossif Strehin, PhD (Allergan), and Phillip Messersmith, PhD (University of California, Berkeley).

"We discovered that the HIF-1a pathway—an oxygen regulatory pathway predominantly used early in evolution but still used during embryonic development—can act to trigger healthy regrowth of lost or damaged tissue in mice, opening up new possibilities for mammalian tissue regeneration," says Heber-Katz, a professor at LIMR who heads the Laboratory of Regenerative Medicine.

The discovery is the latest development in a long investigation sparked by a chance observation in an unusual mouse strain. Almost 20 years ago, Heber-Katz noticed that the MRL mouse can spontaneously regenerate cartilage and other tissues after injury, making it a rare exception among mammals. Years of subsequent research involving the MRL mouse led Heber-Katz and colleagues to theorize that the HIF-1a pathway, which helps cells respond to low oxygen conditions, may also hold the key to the unique regenerative capability of MRL mice.

In the current study, the scientific team focused on the HIF-1a? protein, the expression of which is markedly increased before and after injury in the MRL mouse. Under normal oxygen conditions, HIF-1a is degraded by prolyl hydroxylases (PHDs). Stabilization of HIF-1a levels can be accomplished through inhibition of PHDs.

To test their theory, the researchers first experimentally down-regulated HIF-1a in MRL mice, which they found led to a loss of regenerative capability in the mice. Next, they selected a non-regenerating strain of mice to see what would happen when they experimentally up-regulated

(stabilized) HIF-1a levels after an ear hole punch injury. The mice received three injections of a PHD inhibitor in a slow-release formulation at 5-day intervals. After 30 days, the researchers observed ear hole healing with closure and regrowth of cartilage and new hair follicles. In addition, the drug-treated mice showed a pattern of molecular changes indistinguishable from that observed in MRL mice during regeneration in response to injury, confirming HIF-1a as a central driver of healthy regeneration of lost or damaged tissue in mice.

Heber-Katz notes that unlike other approaches to tissue regeneration, their group found that it was possible to achieve healthy tissue regrowth in a mouse model in situ, without the use of stem cells.

"Our experiment shows the possibility of taking mature cells and, with addition of HIF-1a, causing dedifferentiation to a highly immature state where the cells can proliferate, followed by redifferentiation upon withdrawal of HIF-1a," says Heber-Katz. "Many researchers in the field see tissue regeneration as a very complex set of events, but some of us look at it more as a process that needs to be turned on and allowed to go to completion. This is what is so exciting about what we saw with drug-induced stabilization of HIF-1a."

Heber-Katz and her collaborators plan to move ahead to modify the drug delivery system to achieve an ideal formulation, which they will use to investigate regrowth potential in many types of tissues.

"This remarkable work has vast importance in medicine and surgery and spotlights the diverse and important scientific investigations underway at LIMR," says George Prendergast, PhD, President and CEO of LIMR. "We are committed to the quest to discover therapies that make healthy tissue regeneration a possibility in humans."

More information: Zhang Y, Strehin I, Bedelbaeva K, Gourevitch D,

Medical Xpress

Clark L, Leferovich J, Messersmith PB, Heber-Katz E. Drug-induced regeneration in adult mice. *Sci Transl Med*. 2015;290.
stm.sciencemag.org/lookup/doi/ … scitranslmed.3010228

Provided by Main Line Health, Lankenau Institute for Medical Research

Citation: Study demonstrates drug-induced ear tissue regeneration in mice (2015, June 3) retrieved 9 May 2024 from
https://medicalxpress.com/news/2015-06-drug-induced-ear-tissue-regeneration-mice.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.