Loss of Tumor-Suppressor and DNA-Maintenance Proteins Causes Tissue Demise, Study Finds

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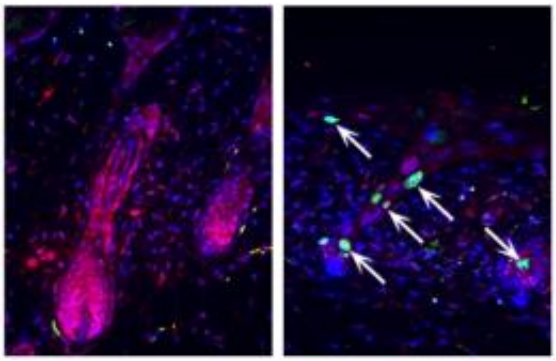

Hair follicle regeneration by undamaged cells (red, left panel) is delayed by the presence of damaged cells (arrows, right panel). Damaged cells are maintained because of the absence of p53 (right panel). Credit: Yaroslava Ruzankina, PhD; David Schoppy; Eric Brown, PhD, University of Pennsylvania School of Medicine

(PhysOrg.com) -- A study published in the October issue of *Nature Genetics* demonstrates that loss of the tumor-suppressor protein p53, coupled with elimination of the DNA-maintenance protein ATR, severely disrupts tissue maintenance in mice. As a result, tissues deteriorate rapidly, which is generally fatal in these animals. In addition, the study provides supportive evidence for the use of inhibitors of ATR in cancer therapy.

Essentially, says senior author Eric Brown, PhD, Assistant Professor of Cancer Biology at the University of Pennsylvania School of Medicine, the findings highlight the fact that day-to-day maintenance required to keep proliferative tissues like skin and intestines functional is about more than just regeneration, a stem cell-based process that forms the basis of tissue renewal. It's also about housekeeping, the clearing away of damaged cells.

Whereas loss of ATR causes DNA damage, the job of p53 is to monitor cells for such damage and either stimulate the early demise of such cells or prevent their replication, the housekeeping part of the equation. The findings indicate that as messy as things can become in the absence of a DNA maintenance protein like ATR, failing to remove resulting damaged cells by also deleting p53, is worse. "Because the persistence of damaged cells in the absence of p53 prevents appropriate tissue renewal, these and other studies have underscored the importance not only of maintaining competent stem cells, but also of eliminating what gets in the way of regeneration," explains Brown.

"An analogy to our findings is what happens to trees during the changing seasons," says Brown. "In springtime, leaves are new and undamaged. But as the summer wears on, the effects of various influences - insects, drought, and disease - cause them to lose the pristine qualities they once had. However, the subsequent fall of these leaves presents a unique opportunity for regeneration later on, a chance to rejuvenate from anew without pre-existing obstacles. Similarly, by suppressing the accumulation of damaged cells in tissues, p53 permits more efficient tissue renewal when ATR is deleted."

Cells without ATR that remain uncleared may be block tissue regeneration either by effectively refusing to relinquish space to undamaged cells, or by secreting signals that halt regeneration until they have been removed.

These results came as something of a surprise, says Brown. Previous studies pairing DNA-repair mutations with p53 mutations always led to a partial rescue of the DNA repair mutation "We think this happens because p53 loss helps cells with just a little DNA damage to continue to contribute to the tissue" says Brown. So at a minimum, the team expected nothing to happen.

"But we got the opposite result: Absence of p53 did not rescue the tissue degeneration caused by ATR loss, it made it much worse. This result suggested that allowing mutant cells without ATR to persist is more harmful to tissues than eliminating them in the first place." Brown speculates that could be because the ATR mutation produces much more damage than most other DNA-repair defects.

According to Brown, their findings and those of other laboratories also reinforce the potential of a new therapeutic for cancer. That's because, among their other discoveries, the team noticed that cells missing both ATR and p53 have more DNA damage than those missing either gene alone. As a large fraction of human cancers have p53 mutations, he says, "p53-deficient tumors might be especially susceptible to ATR inhibition." Indeed, clinical trials already are underway involving an ATR partner protein called Chk1. "Our study provides supportive evidence for the potential use of ATR/Chk1 inhibitors in cancer therapy," says Brown.

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Provided by University of Pennsylvania (news : web)