New clue to controlling skin regeneration -- as well as skin cancer

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How do organs "know" when to stop growing? The answer could be useful in regenerative medicine, and also in cancer - where these "stop growing" signals either aren't issued or aren't heeded. Researchers in the Stem Cell Program at Children's Hospital Boston have now found a regulator of gene activity that tells epidermal stem cells when it's time to grow more skin, as well as a "crowd control" molecule that can sense cell crowding and turn the growth off.

The work, in mice and in human cancer cells, provides clues to new therapeutic strategies for cancer, particularly squamous cell carcinoma, the second most common skin cancer, in which epidermal cell growth is inappropriately turned on. It could also aid efforts to grow skin grafts and treat burn patients.

The findings, published in *Cell* on March 4, underscore the idea that cancer and regeneration are closely related. "We have found a molecular switch that tells your skin to keep growing or stop growing," says Fernando Camargo, PhD, the study's senior investigator and a principal investigator in Children's Stem Cell Program.

Camargo and colleagues manipulated a molecule called Yap1, already known - from studies in fruit flies - to cause massive tumor growth by triggering a pathway known as Hippo (so named because of the enormous size of the tumors). When they suppressed Yap1 function in mice, their epidermal skin stem cells failed to expand and they had thin, fragile skin.

The opposite was also true. "The more Yap1 you have in your stem cells, the thicker your skin grows," says Camargo, who is also a member of the Harvard Stem Cell Institute.

However, activation of Yap1 also caused the mice to develop squamous-cell carcinoma-like tumors, the researchers found.

They further showed that Yap1 is inactivated by a known tumor suppressor called alpha-catenin, which binds to Yap1 and keeps it outside the cell nucleus. In both mice and human squamous carcinoma cells with alpha-catenin mutations, Yap1 returns to the nucleus and becomes active again.

"Alpha catenin is silenced in many types of epithelial cancer - skin cancer, colon cancer and other squamous cell cancers," says Camargo. "When alpha catenin is absent or mutated, you get an overgrowth of cells, but until now it was unclear why. Our work suggests that over-activation of Yap 1 is likely what drives these cancers."

Alpha-catenin is known to be able to sense the density of cells in its immediate environment, and perhaps even their type. Camargo's team revealed how the information is used: When cells are packed too tightly, alpha-catenin inhibits Yap1 - the first demonstration of a direct link between an environmental cue (cell density) and a molecular regulator of organ size. Until now, little has been known about what maintains organs at a specific size.

"Through Yap1, alpha-catenin tells epidermal stem cells to either proliferate or not proliferate, depending on the needs of the tissue," Camargo explains.

Now that the "switch" for skin growth is known, manipulating it could provide ways to grow skin cells when they're needed or, conversely, to stop cancerous growth. Camargo's group is conducting screening tests to find small molecules that mimic Yap1, to induce skin regeneration at the site of a wound, or that inhibit Yap1 to treat skin tumors. The team is also looking for other molecules that may also interact with Yap1.

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