Nature Reviews Molecular Cell Biology | Published online 16 Aug 2017; doi:10.1038/nrm.2017.85

CANCER BIOLOGY

The skin's power of elimination

The skin can harbour mutant, potentially malignant cells without developing cancer. Greco, Beronja and colleagues now show that this tolerance can be explained, at least in part, by the remarkable ability of the skin to counteract malignant growth by efficiently eliminating abnormal tissue structures.

> the skin can efficiently restore normal tissue architecture

To understand the basis of the skin's apparent ability to resist cancer, the authors focused on the WNT signalling pathway, which when mutated, is known to promote tumorigenic tissue overgrowth in several tissues, including the skin. They introduced activating mutations to β-catenin — an effector of the WNT pathway — in a small population of epithelial stem cells in mouse skin *in vivo* and imaged them over time using intravital microscopy.

Getty/Gandee Vasan

As expected, cells with activated β-catenin induced abnormal tissue outgrowths. However, most of these outgrowths fully regressed within 4 weeks. The outgrowths that were not resolved comprised predominantly wild-type cells and were later converted into functional skin appendages (such as hair follicles or sebaceous glands). Challenging the tissue by introducing a much larger population of mutant β-catenin cells led to the formation of large skin tumours, but, stunningly, these outgrowths were also successfully eliminated or converted to functional epithelial appendages. The skin was also able to efficiently resolve aberrant phenotypes that were induced by the hyperproliferative mutation in the proto-oncogene *Hras* and even by tissue injury. Thus, the ability of the skin to counteract aberrant growth and resolve deformations seems to be a conserved property of this tissue.

In the β-catenin-activated tissue, outgrowths of mutant cells were consistently surrounded, and eventually became enveloped, by wild-type cells, suggesting that healthy cells contribute to the elimination of mutant cells and can limit the abnormal tissue growth. Indeed, inhibiting wild-type cell proliferation or their recruitment to tissue outgrowths considerably decreased the ability of the skin to eliminate aberrant cells, and many of the outgrowths persisted and later developed into cysts.

In summary, in the event of tissue deformation, the skin can efficiently restore normal tissue architecture, which, at least in the presence of ectopic tissue outgrowths, occurs by eliminating abnormal cells with the involvement of wild-type cells. It will be important to study the mechanisms that enable tissue overgrowth to be sensed and resolved, and to exploit this knowledge to counteract malignancy in epithelial tissues.

Paulina Strzyz

ORIGINAL ARTICLE Brown, S., Pineda C. M. *et al.* Correction of aberrant growth preserves tissue homeostasis. *Nature* http://dx.doi.org/10.1038/nature23304 (2017)