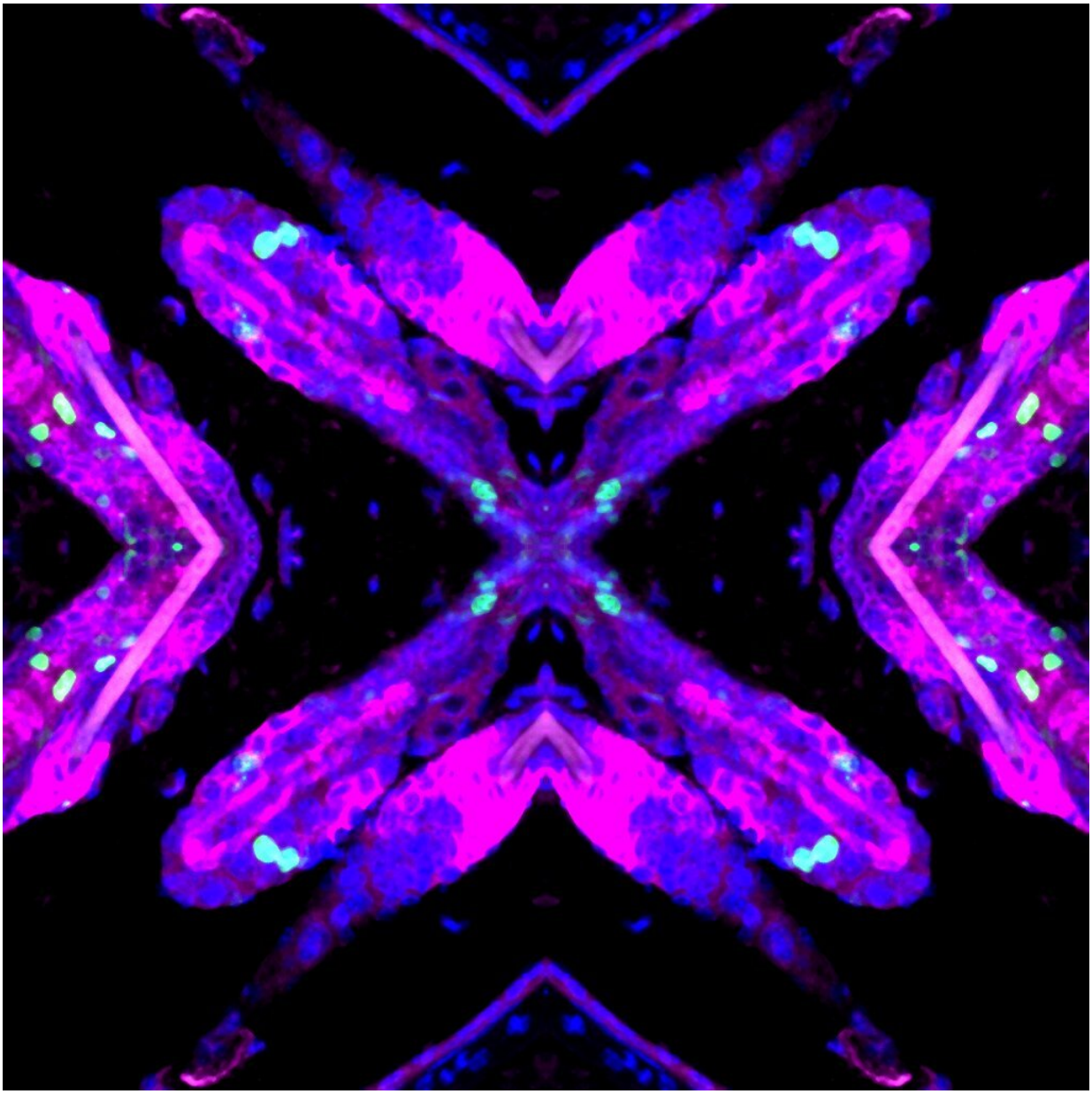
Skin in balance: Joint forces of polarity and cell mechanics

July 31 2019



A digitally processed micrograph of mouse skin and hair follicles, with DNA damage (green) in the skin epithelium, including the hair follicle stem cells (purple). Blue depicts cell nuclei. Credit: Martim Dias Gomes

The cell polarity protein Par3 controls mechanical changes in the skin and plays an important role in cell division. Malfunction can lead to DNA damages. The balance of the system is of great importance—while too much differentiation leads to loss of stem cells and therefore premature aging, too many cell divisions can be a cause of skin cancer. The new study by a team around Sandra Iden about how polarity regulators control cellular mechanics in the skin has now been published in *Nature Communications*.

The skin serves as a crucial barrier to the outside world. Its task is not only to keep pathogens and toxic chemicals out of the body, but also to keep water inside and maintain hydration. In order to function properly, the skin epidermis needs a constant balance of cells as they are shed off and replenished. The skin epidermis is made up of several layers with different functions. Skin stem cells are responsible for the self-renewing capacity of the skin.

In a previous study, the researchers showed that inactivation of the polarity protein Par3 resulted in a decline of stem cells, impaired skin homeostasis and caused premature skin aging. Back then, however, the underlying mechanisms remained unclear. "We are now able to show that Par3 has a direct influence on the homeostasis of the skin by controlling the mechanical properties of keratinocytes, the main skin epithelial cell," said leading scientist Dr. Sandra Iden. The polarity protein Par3 controls the mechanical properties of the main skin epithelial cells, called keratinocytes. It has functions that are highly conserved across species. Par3 also regulates barrier function and cell

division orientation.

The recent work started with two separate approaches. Co-first author Martim Dias Gomes said, "We realized that inactivating Par3 leads to failures in cell divisions, resulting in DNA damage responses." At the same time, his colleague and co-first author Soriba Letzian were working on another project: "We challenged mouse skin with UV light—but observed an unexpected DNA damage response in absence of UV when Par3 was missing. That was the moment we realized that the DNA damage response and the aberrant cell divisions might be tightly linked," he said. Based on these results, they teamed up and together examined possible causes of these mitotic failures.

As they now show, Par3 is an important regulator of contractility of keratinocytes, which is required to maintain the accuracy of cell division events. The absence of Par3 led to mitotic errors, causing an alert signal and a cascade of DNA damage responses that then fueled premature differentiation, and potentially skin stem cell decline. These findings were surprising, as during the development of epithelial tissues Par3 was considered to serve tissue function rather through orienting mitotic spindles.

These new findings thus reveal that core polarity proteins like Par3 steer mechanochemical networks essential to a healthy self-renewal capacity. "We are glad that we were able to contribute a piece of the puzzle of how the skin epithelium is maintained intact, and hope that this will serve future medical applications," Sandra Iden says.

More information: Martim Dias Gomes et al, Polarity signaling ensures epidermal homeostasis by coupling cellular mechanics and genomic integrity, *Nature Communications* (2019). DOI: 10.1038/s41467-019-11325-3

Provided by University of Cologne