CNIO scientists discover a novel molecular mechanism involved in the formation of the skin

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The formation of human skin involves a cascade of biochemical signals, which are not well understood. However, they are very important since their failure may cause diseases, such as Atopic Dermatitis and skin cancers, which affect more than 25% of the human population. CNIO researchers now discovered a new mechanism that regulates the differentiation of keratinocytes, the cells that make up most of the epidermis of the skin. Additionally, they show that this mechanism might be involved in skin cancer.

Specifically, researchers identify Fra-2, an AP-1 transcription factor, as a key regulator for the differentiation of keratinocytes: if Fra-2 is not activated, epidermal differentiation fails and the skin does not properly form. The study is published this week in the journal *Genes & Development*, featured on the cover page with Stefanie Wurm as first author; the study is directed by Erwin Wagner, head of the BBVA Foundation-CNIO Cancer Cell Biology Program.

Human keratinocytes live approximately one month, when they go through a maturation process arising from the innermost epidermal stem cell layer and move up to the body surface. In technical terms, this process is called keratinocyte differentiation. As the authors write "in the epidermis, the induction of keratinocyte differentiation is essential for the acquisition of the barrier function of the skin, as well as tissue homeostasis [stability]".

In recent years a number of biochemical processes involved in the differentiation of keratinocytes have been identified. Today we know that a plethora of genes localized in the Epidermal Differentiation Complex (EDC) are necessary for epidermal differentiation. The expression of these genes is regulated by the coordinated interaction of a diverse set of proteins, among them transcription factors.

The work now published shows that Fra-2, one of these transcription factors, plays a key regulatory role. "With the help of specific mouse models we demonstrate that the expression of Fra-2 in keratinocytes induces the expression of genes in the EDC," the authors write.

Conversely, loss of Fra-2 in suprabasal keratinocytes was sufficient to cause skin barrier defects, due to reduced expression of EDC genes. The authors also found a possible link to cancer. In mice prone to develop benign skin tumors -papillomas-, the activation of Fra-2 reduced skin tumor burden. The authors demonstrate that Fra-2 induces premature differentiation of keratinocytes.

An additional novelty is related to the regulation of the transcriptional activity of Fra-2. The work reveals that the activation of this transcription factor depends on chemical protein modifications and the interaction with two important enzymes, Ezh2 and ERK1/2. This mode of activation was not known, and the researchers now plan to study whether this novel mechanism is also involved in other processes.

"We describe a novel interaction of Fra-2 with Ezh2," says Stefanie Wurm. "Using mass spectrometry approaches, we identified a novel post-translational modification of Fra-2: when methylated by Ezh2 [methylation is a chemical modification when the molecule gains a methyl group], Fra-2 remains inactive in basal cells and when it is phosphorylated by ERK1/2 [addition of a phosphate group], it becomes active."

These findings open new avenues to explore "if this switch is a general mechanism of transcription

factor activation," continues Wurm. "We also want to study whether inhibition of Ezh2 may be a valuable therapeutic strategy for skin diseases related to keratinocyte differentiation defects."

More information: Terminal epidermal differentiation is regulated by the interaction of Fra-2/AP-1 with Ezh2 and ERK1/2. Stefanie Wurm, Jisheng Zhang, Juan Guinea-Viniegra, Fernando Garcia, Javier Muñoz, Latifa Bakiri, Elena Ezhkova, and Erwin F. Wagner. *Genes & Development* (2015). DOI: 10.1101/gad.249748.114

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