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Protein 'switch' suppresses skin cancer development

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The protein IKKalpha (IKKα) regulates the cell cycle of keratinocytes and plays a key role in keeping these specialized skin cells from becoming malignant, researchers at The University of Texas M. D. Anderson Cancer Center report in the Sept. 9 issue of *Cancer Cell*.

"We have shown that IKKα acts as a sentry, monitoring and, when necessary, halting proliferation of these important cells. In the first mouse model of its kind, we also found that deleting IKKα spontaneously induced squamous cell carcinomas by activating the epidermal growth factor receptor pathway," said senior author Yinling Hu, Ph.D., assistant professor in M. D. Anderson's Department of Carcinogenesis at the Science Park - Research Division in Smithville, Texas. "These results provide new therapeutic targets for prevention of skin cancer."

Keratinocytes originate in the basal layer of the epidermis to replace skin cells at the surface that have been shed. As keratinocytes gradually move up through the skin layers, they differentiate and eventually form the top layer of the skin, which is composed of squamous cells. The cycle ends through terminal differentiation, in which cells lose their ability to reproduce by dividing in two. They eventually die.

Hu and colleagues reported in research last year that a reduction in IKKα expression promotes the development of chemically induced papillomas and carcinomas, which are benign and malignant tumors of the epithelium respectively. Epithelial cells make up the outer layers of skin

and the inner linings of many organs, including the lungs and the gastrointestinal, reproductive and urinary tracts. Most cancers originate in organ epithelial cells. The researchers also demonstrated that an intact IKKα gene is required to suppress skin cancer development.

Downregulation of IKKα has been noted in a variety of human squamous cell carcinomas, including those of the skin, esophagus, lungs, and head and neck.

IKKα's role in maintaining skin homeostasis, or stability, had remained unclear because an appropriate mouse model was not available. To solve this problem, Bigang Liu, the first author, and colleagues generated mice with IKKα deletions in their keratinocytes.

In a series of experiments, Hu's group found evidence that IKKα functions as a sentry that monitors keratinocyte proliferation and then induces terminal differentiation. In one experiment, within a few days of birth, mutant mice had developed thickened and wrinkled skin and gradually showed retarded development. The researchers also found that even a low level of IKKα in the epidermis was sufficient to allow normal embryonic skin development.

The researchers examined the signaling pathways involved in overproliferation and reduced differentiation in IKKα -deficient cells. In one, they found that IKKα turns down a cellular signaling loop that activates EGFR and other growth factors previously found to regulate keratinocyte proliferation and differentiation.

Another experiment demonstrated that IKKα deletions in keratinocytes cause skin carcinomas and that inactivating EGFR reverses this process in the mutant mice. Furthermore, either inactivation of EGFR or reintroduction of IKKα inhibited excessive cell division, induced terminal differentiation, and prevented skin cancer by repressing the

EGFR-driven signaling loop.

Hu's group concluded that IKKα is a switch for proliferation and differentiation and is essential to maintaining skin homeostasis, or stability, and preventing skin cancer.

"This study has revealed the importance of IKKα in maintaining skin homeostasis and in preventing skin cancer, as well as the mechanism of how IKKα acts in these processes," Hu said. "We will further investigate how IKKα deletion targets a single cancer initiation cell, which will provide new avenues to treat cancer."

Source: University of Texas M. D. Anderson Cancer Center