Skin cancer marker plays critical role in tumor growth

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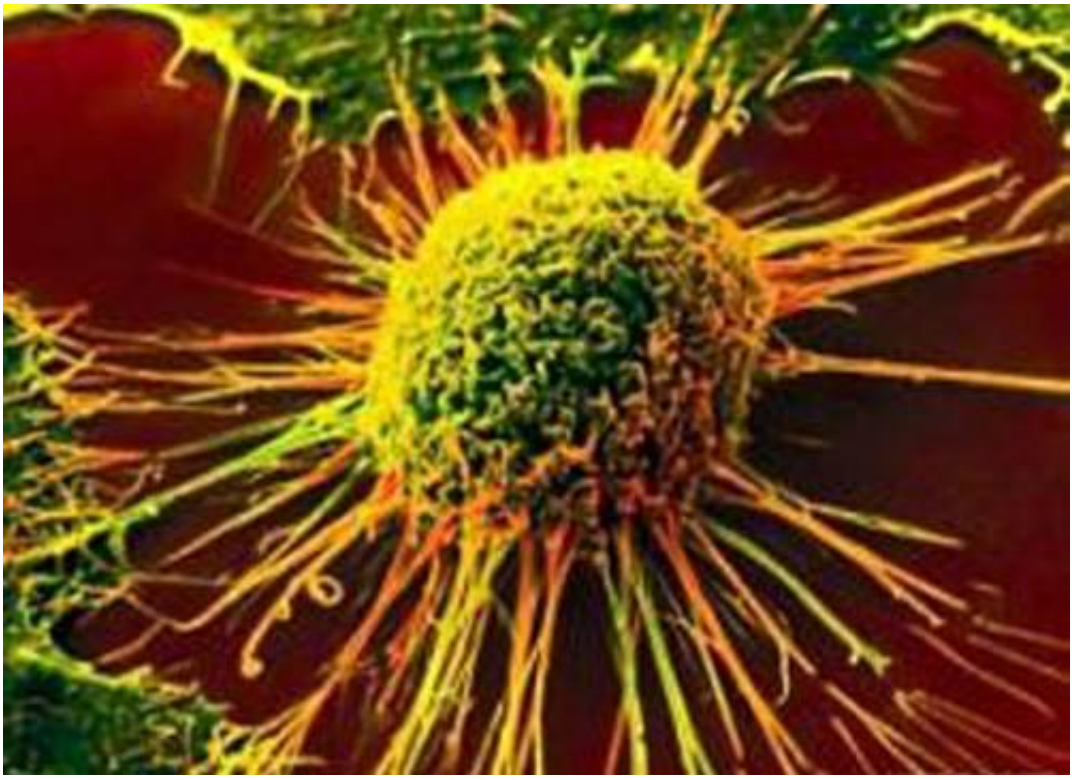

New research from the Johns Hopkins Bloomberg School of Public Health suggests that the protein keratin 17 - the presence of which is used in the lab to detect and stage various types of cancers - is not just a biomarker for the disease, but may play a critical role in tumor growth.

This new understanding of how keratin 17 works, the researchers say, could lead to the development of better ways to detect and prevent cancer, and identify new targets for therapeutic treatment. A report on the findings is published July 13 in *Nature Genetics*.

"Keratin 17 is a sensitive marker for various cancers and several other acute and chronic diseases affecting the skin, but we didn't know whether it was a driver of the disease or just an innocent bystander," says study lead author Ryan P. Hobbs, PhD, a postdoctoral fellow in the Bloomberg School's Department of Biochemistry and Molecular Biology. "We didn't know if the keratin was actually involved in the onset and promotion of skin tumors or if it was just along for the ride. This research, focused on models for cancer affecting the skin, tells us it's more of a driver than a passenger."

Keratin 17 is found in healthy hair follicles, fingernails and glands, but not in healthy epidermis, the outermost layer of the skin. It emerges, however, in basal cell skin cancers and most squamous cell cancer, and its appearance in such settings precedes the actual onset of tumor growth . Other researchers have determined that the quantity of keratin 17 present in other types of tumors such as in the breast, cervix, lung and pancreas can indicate how aggressive it is and help determine a patient's prognosis.

Hobbs and his colleagues say keratin 17 doesn't cause the cancer itself, but promotes an inflammatory and immune response that can allow the disease to develop more aggressively.

"Keratin 17 is like a throttle pedal," says the study's senior author Pierre A. Coulombe, PhD, E.V. McCollum professor and chair of the Bloomberg School's Department of Biochemistry and Molecular Biology. "It drives a specific type of sustained inflammation that helps a cancer become a cancer."

For their study, the researchers worked with mice genetically engineered to develop skin cancer, in this case viral HPV-induced squamous cell carcinoma, building on Coulombe's prior research in basal cell carcinoma, the most common form of skin cancer. When the researchers examined these models in the complete absence of keratin 17, the onset of the expected tumors was significantly delayed, correlating with a significantly dampened inflammatory and immune response. Importantly, the researchers were able to repeat the experiment in human tumor cells with a similar result.

Analyzing both mouse and human samples, the researchers determined that keratin 17 can move to the nucleus of tumor cells, and cause specific tumor-promoting inflammatory and immune response genes to be turned on. Contributing to the discovery of keratin 17's presence in the nucleus was Justin Jacob, a doctoral student in the laboratory and a co-author on the study. Until then, keratin 17 was believed to function exclusively outside of the nucleus as a component of the cytoskeleton, which provides a cell with its shape and function.

The researchers also found that a protein called Aire (autoimmune regulator) interacts with keratin 17 in the nucleus of tumor skin cells. This represents yet another unexpected finding, as Aire is known to be a key player in the thymus, where it is essential in preventing the host's immune system from attacking itself. When the Aire gene was deleted, tumor formation was also delayed in mouse skin.

Hobbs and Coulombe say the ability to delay tumor formation could buy the necessary time for either the immune system to do its job and prevent tumors from growing or for anti-cancer medications to fight tumors that do form.

"A better understanding of what drives the onset, growth and characteristics of tumors will ultimately help us develop better

biomarkers and treatments," Hobbs says.

More information: "Keratin-dependent regulation of Aire and gene expression in skin tumor keratinocytes" *Nature Genetics*, DOI: 10.1038/ng.3355

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