Unraveling the genetic causes of skin cancer

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Skin cancer is on the rise in the United States. Squamous cell carcinoma, the second most common form of cancer in the U.S., has the highest mortality rate of all non-melanoma skin cancers. In roughly two to five percent of patients, the disease will metastasize and spread throughout the body, making it difficult to treat.

American University Associate Professor of Biology Katie DeCicco-Skinner and her colleagues are helping to identify the genetic factors that lead to squamous cell carcinoma. In a new paper, they show how the interaction between a cell signaling pathway called MET and a gene, Tpl2, contributes to skin cancer progression. Their findings indicate a potential target for therapies that could help those suffering from advanced squamous cell carcinoma for whom treatments like radiation and chemotherapy are not options.

"It's critical we obtain a better understanding of the biological mechanisms by which skin cancers develop," DeCicco-Skinner said. "The incidence of all skin cancers has drastically increased over the last several decades and yet much is still unknown about the genetic causes that lead to development or progression of these cancers."

Using animal models, DeCicco-Skinner researches how skin cancers develop. In 2011 she and her colleagues revealed how the loss of Tpl2 increased susceptibility to skin tumor development. In that study, Tpl2 was deleted in mice. Without the gene, the mice developed a significantly higher number of tumors and showed biomarkers of cancer, such as increased inflammation and skin cells turning invasive and attacking healthy cells. Tpl2's role in cancer is far from clear, however. It works as an oncogene for some cancers, and a tumor suppressor for others, depending on the tissue in which the signal is altered, DeCicco-Skinner said. In squamous cell carcinoma, Tpl2 acts as a tumor suppressor.

In the new paper, published in *Oncogenesis*, DeCicco-Skinner and her team dig deeper: what is it about the loss of Tpl2 that's causing benign skin tumors to convert into squamous cell carcinoma? Part of the answer, it turns out, is the cell signaling pathway MET. MET is known to play a role in many cancers. Activation of MET contributes to many different aspects of skin cancer progression, including survival, invasion, angiogenesis, and drug resistance.

In a controlled study, knockout mice (those mice without the gene Tpl2) were treated with Capmatinib, a drug currently being tested in clinical trials to treat a variety of cancers, and which blocks MET from activating. The study results showed a 60 percent reduction in tumors in the mice. More importantly, the tumors stayed benign. Therefore, lack of the Tpl2 gene results in an overexpression of MET, which is, in part, the cause of squamous cell carcinoma, the researchers concluded.

As a receptor, MET activates a wide range of signal transduction pathways. If it gets activated, it turns on proteins in a cascading effect. What results is cell dysregulation: the cell divides quicker, is more invasive, and becomes more inflammatory.

While MET is a significant player in skin cancer progression, it's not the only one, DeCicco-Skinner points out. Future studies will dive into the relationship between MET and other receptors to further explore its aberrant signaling.

Cell signaling pathways are complicated. Patients with advanced cancer disease are often treated with medicinal cocktails to keep cancer from spreading throughout the body. "But it can be like the game of Whac-A-Mole," DeCicco-Skinner explains, "in that, when one protein gets knocked down, sometimes compensation occurs and another one pops up. We need to understand the interactions between different proteins, so we can identify how to most effectively target the

development and spread of cancers such as squamous cell carcinoma."

More information: Nicole F. Bonan et al, Inhibition of HGF/MET signaling decreases overall tumor burden and blocks malignant conversion in Tpl2-related skin cancer, *Oncogenesis* (2019). DOI: 10.1038/s41389-018-0109-8

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