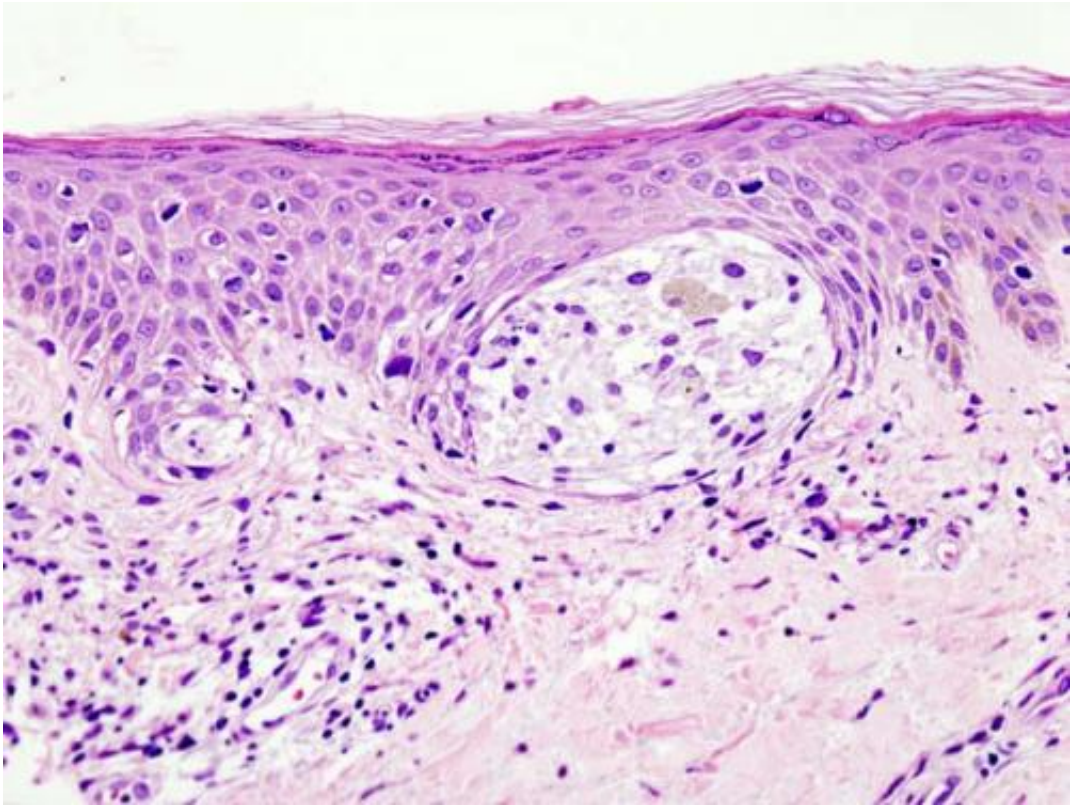
Study finds new potential melanoma drug target

May 2 2015



Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

A new treatment for melanoma could be on the horizon, thanks to a finding by a UNC Lineberger Comprehensive Cancer Center-led team. In the study, which was published online today in the journal *Clinical Cancer Research*, the authors report that they found high levels of an

enzyme in melanoma samples that they believe is a potential drug target.

UNC Lineberger Comprehensive Cancer Center researchers have identified a possible new drug target for a potentially deadly form of skin cancer that, when blocked in a pre-clinical study in mice, reduced the cancer's growth.

The researchers found high levels of a particular enzyme in melanoma samples that they believe is a driver of the cancer's growth. The enzyme, called interleukin-2 inducible T-cell kinase, or ITK, has not previously been explored as a driver of solid tumors. Normally, it's expressed in a subset of the body's disease-fighting immune cells.

The researchers hope the findings, which were published today in the journal *Clinical Cancer Research*, could lead to new treatments for melanoma since, as the researchers state, one drug that can block ITK's activity has been approved for blood cancers and others are in the pipeline for other diseases.

"We have discovered that ITK is highly expressed in melanoma even though it was thought to be restricted to immune cells, and when you inhibit it, you decrease melanoma growth," said Nancy E. Thomas, MD, PhD, a UNC Lineberger member, the Irene and Robert Alan Briggaman Distinguished Professor in the UNC School of Medicine Department of Dermatology and the paper's senior author. "Therefore, we think it's a good potential drug target."

There is a need for new treatment targets for melanoma, a deadly disease once it's started to spread. Melanoma of the skin has a 98 percent five-year survival rate when the cancer is localized, according to data from the National Cancer Institute Surveillance, Epidemiology and End Results Program. But once the cancer has spread regionally, the five-year-survival rate falls to 64 percent. And the survival rate falls to 16

percent after the cancer has spread to more distant regions.

"New therapies are needed because of the high mortality rate for metastatic melanoma, and the ability of melanomas to become resistant to many of the current therapies," said Craig Carson, PhD, a research instructor in the UNC School of Medicine Department of Dermatology and the paper's first author. Carson said they hope their recent finding will lead to new treatments for melanoma.

In an analysis of normal skin tissue, non-cancerous moles, and melanoma samples, researchers found that ITK was expressed at greater levels in primary and metastatic melanomas than in non-cancerous moles. In the metastatic melanoma samples, 91 percent had higher expression levels than of the non-cancerous moles.

The finding was surprising to the researchers because the ITK enzyme is typically expressed only in certain cells in the body.

"It's only found in a subset of the immune cells," Carson said.

ITK helps with the development of certain immune cells, the researchers say, and is involved in immune cell activation, development and production.

"The cancerous cells were packed with that protein, and it was bizarre – that's not supposed to be there," Thomas said. "And so, the question is, well, what is it doing there?"

They found that the gene's expression in the melanoma cells was a driver of the cancer. When they manipulated cells in the test tube to have lower ITK expression, they found that the cells reproduced more slowly and with less movement. They also found that an experimental inhibitor of the ITK protein's activity had the same effect on cells and slowed tumor

growth in mice with melanoma.

They hope their findings will lead to development of treatments for melanoma.

"ITK has been conceived of as a therapeutic target for inflammatory diseases such as chronic obstructive pulmonary disorder, but because ITK had not been noted in melanoma before, it has not been a target for its treatment," Carson said. "I expect ITK to become an important therapeutic target for melanoma because of the expected minimal side effects, and the fact that ITK is found in so many of the melanomas we have investigated."

More information: Carson C.C., Moschos S.J.,Edmiston S.N., Darr D.B., Nikolaishvili-Feinberg N, Groben PA, Zhou X, Kuan PF, Pandey S, Chan KT, Jordan JL, Hao H, Frank JS, Hopkinson DA, Gibbs DC, Alldredge VD, Parrish E, Hanna SC, Berkowitz P, Rubenstein DS, Miller CR, Bear JE, Ollila DW, Sharpless NE, Conway K, Thomas NE. IL-2 Inducible T-cell Kinase, a Novel Therapeutic Target in Melanoma. *Clinical Cancer Research*. DOI: 10.1158/1078-0432.CCR-14-1826

Provided by University of North Carolina at Chapel Hill School of Medicine