Melanoma mutation rewires cell metabolism

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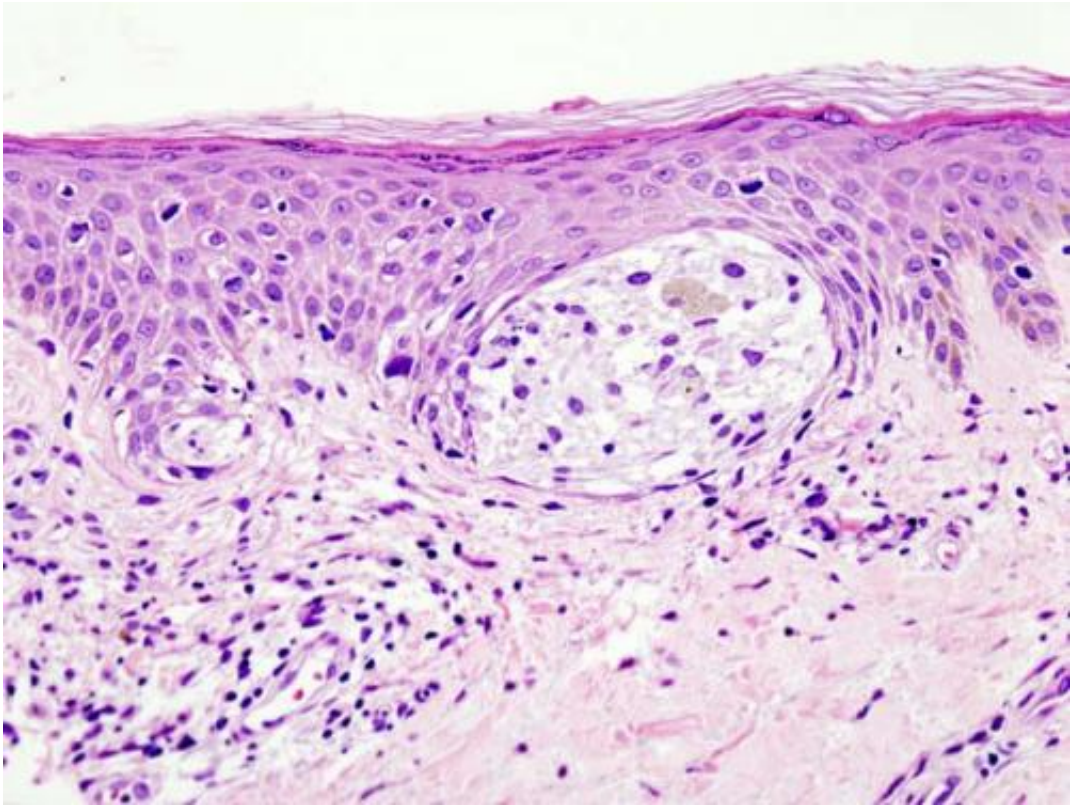

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

A mutation found in most melanomas rewires cancer cells' metabolism, making them dependent on a ketogenesis enzyme, researchers at Winship Cancer Institute of Emory University have discovered.

The finding points to possible strategies for countering resistance to

existing drugs that target the B-raf V600E mutation, or potential alternatives to those drugs. It may also explain why the V600E mutation in particular is so common in melanomas.

The results are scheduled for publication in *Molecular Cell*.

The growth-promoting V600E mutation in the gene B-raf is present in most melanomas, and also in some cases of colon and thyroid cancer. Drugs such as vemurafenib are available that target this mutation, but in clinical trials, after a period of apparent remission, cancers carrying the V600E mutation invariably develop drug resistance.

Researchers led by Jing Chen, PhD and Sumin Kang, PhD found that the B-raf V600E mutation stimulates cancer cells to produce more of the enzyme HMG-CoA lyase, and that melanoma cells with the V600E mutation are dependent on that enzyme, while other melanoma cells are not.

HMG-CoA lyase is part of the ketogenesis pathway, which allows the body to break down fats for energy when glucose levels in the blood are low. Ketogenesis can be activated by a low-carbohydrate, high-fat diet, and usually takes place in the liver. However, the B-raf V600E mutation appears to be turning on ketogenesis in the cancer cells.

One of the alternative energy sources generated through ketogenesis is acetoacetate, whose levels are controlled by HMG CoA lyase. Acetoacetate combines with the B-raf V600E mutation to stimulate proliferation, the researchers found.

"This combination effect provides an explanation for why V600E is the predominant mutation of B-raf in human cancers," Chen says.

Many possible random mutations occurring in pre-cancerous cells could

affect B-raf. This one particular mutation seems to give a pre-cancerous cell an evolutionary advantage, Chen says. The V600E mutation alters the structure of B-raf, so that acetoacetate both binds B-raf and promotes B-raf's oncogenic signaling. Elevated acetoacetate seems to act as a positive feedback mechanism accelerating growth.

Drugs that inhibit HMG-CoA lyase or compete with acetoacetate could be alternatives to or counter resistance to drugs such as vemurafenib, which target the V600E-mutated form of B-raf. Efficacy and toxicity would need to be tested.

"Our results support an emerging concept in cancer metabolism where particular mutations rewire metabolic pathways in cancer cells, in a manner that is distinct from the general Warburg effect favoring glycolysis," Chen adds.

Most of the paper's experiments were performed on human melanoma cells in culture or injected into mice. To show that the metabolic changes they discovered were clinically relevant, researchers tested hairy cell leukemia (a form of leukemia caused by the B-raf V600E mutation) cells obtained directly from patients and found elevated levels of HMG-CoA lyase and acetoacetate, compared to control cells.

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