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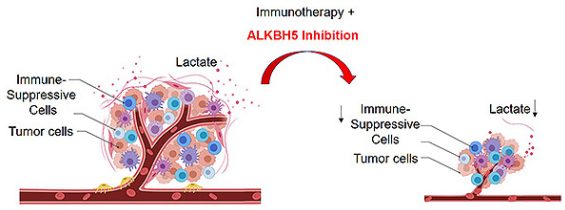
Inhibiting Enzyme Helps Cancer Immunotherapy Work Better

People with inactive RNA-editing enzyme respond better to immunotherapy; inhibitors of the enzyme help mice with difficult-to-treat cancers live longer

Cancer immunotherapy — a treatment that better enables a patient's own immune system to attack tumors — has shown great potential against some cancers. Yet immunotherapy doesn't work against all tumor types, and many patients who initially respond later develop resistance and relapse.

Researchers at University of California San Diego School of Medicine and Moores Cancer Center are trying to understand why that is, and how to overcome the hurdles to improve cancer immunotherapy.



UC San Diego researchers found that when the enzyme ALKBH5 is inhibited during cancer immunotherapy, metabolites in the tumor microenvironment change is such a way that fewer immune-suppressing cells accumulate, making the treatment more effective at shrinking tumors.

In a study published August 3, 2020 in *Proceedings of the National Academy of Sciences*, the team uncovered an enzyme that, when inhibited, sensitizes mouse models of cancer to immunotherapy and helps them live longer. What's more, patients with melanoma respond better to immunotherapy if they have natural genetic mutations that inactivate the same enzyme.

Senior author Tariq Rana, PhD, professor and chief of the Division of Genetics in the Department of Pediatrics, explains the findings:

What motivated this study?

My lab is interested in mRNA and its role in many diseases. Let me take a step back: Genes (DNA) are transcribed into mRNA, which is then translated into proteins, the molecules that make up the majority of our cells. But it's not always so straightforward. mRNAs may be

modified by chemical groups that influence whether or not they will be translated. These mRNA modifications are deposited, removed and interpreted by enzymes called writers, erasers and readers. The most abundant mRNA modification in many species, including humans, is known as N6-methyladenosine, or m6A.

We were interested in exploring the role of m6A and its eraser enzyme — called ALKBH5 — in cancer and immunotherapy. To do that, we used CRISPR gene editing to remove the ALKBH5 enzyme in mouse tumor cells, and waited to see what would happen.

In a nutshell, what did you find?
With ALKBH5 gone, immunotherapy worked better in mouse models of difficult-to-treat melanoma and colon cancers. Treated tumors shrunk by an average of approximately 40 to 70 percent and mouse survival was prolonged, compared to mice with normal ALKBH5. We also developed small molecule inhibitors of ALKBH5 and they had a similar effect as genetic removal of the enzyme.

Could this work for people, too?
To answer that question, we collaborated with Sandip Pravin Patel, MD, a medical oncologist and co-leader of experimental therapeutics at Moores Cancer Center at UC San Diego Health. Together we analyzed natural ALKBH5 gene mutations in tissue samples from 359 patients with melanoma.

Consistent with our mouse results, we found that people who happened to have inherited a gene mutation that deletes the ALKBH5 enzyme respond better to anti-PD-1 therapy, a type of cancer immunotherapy, than those with normal ALKBH5. 80 percent of ALKBH5-deficient patients experienced complete or partial response to anti-PD-1 therapy, compared to approximately 50 percent of patients with functioning ALKBH5.

That natural experiment gives us hope that if we can develop our ALKBH5 inhibitors into new medicines for people, we'll one day be able to offer an improved combination treatment — immunotherapy plus an ALKBH5 inhibitor.

How does ALKBH5 get in the way of immunotherapy?
Our mouse studies helped us uncover a likely mechanism. It seems ALKBH5's enzymatic activity leads to changes in the metabolites, byproducts of metabolism such as lactate, in the tissues that surround a tumor. In turn, those metabolites help suppressive immune cells accumulate, allowing tumors to thrive. That's why taking ALKBH5 out of the picture is beneficial — tumors can't progress as well without it.

What's next?

Next we want to look for more targets like ALKBH5 — genes and proteins we can inhibit to give immunotherapy more of an advantage over tumors. We are also optimizing our ALKBH5 inhibitors for future clinical trials.

Co-authors of the study also include: Na Li, Yuqi Kang, Lingling Wang, Sarah Huff, Rachel Tang, Hui Hui, Kriti Agrawal, UC San Diego; Gwendolyn Michelle Gonzalez, Yinsheng Wang, UC Riverside.

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