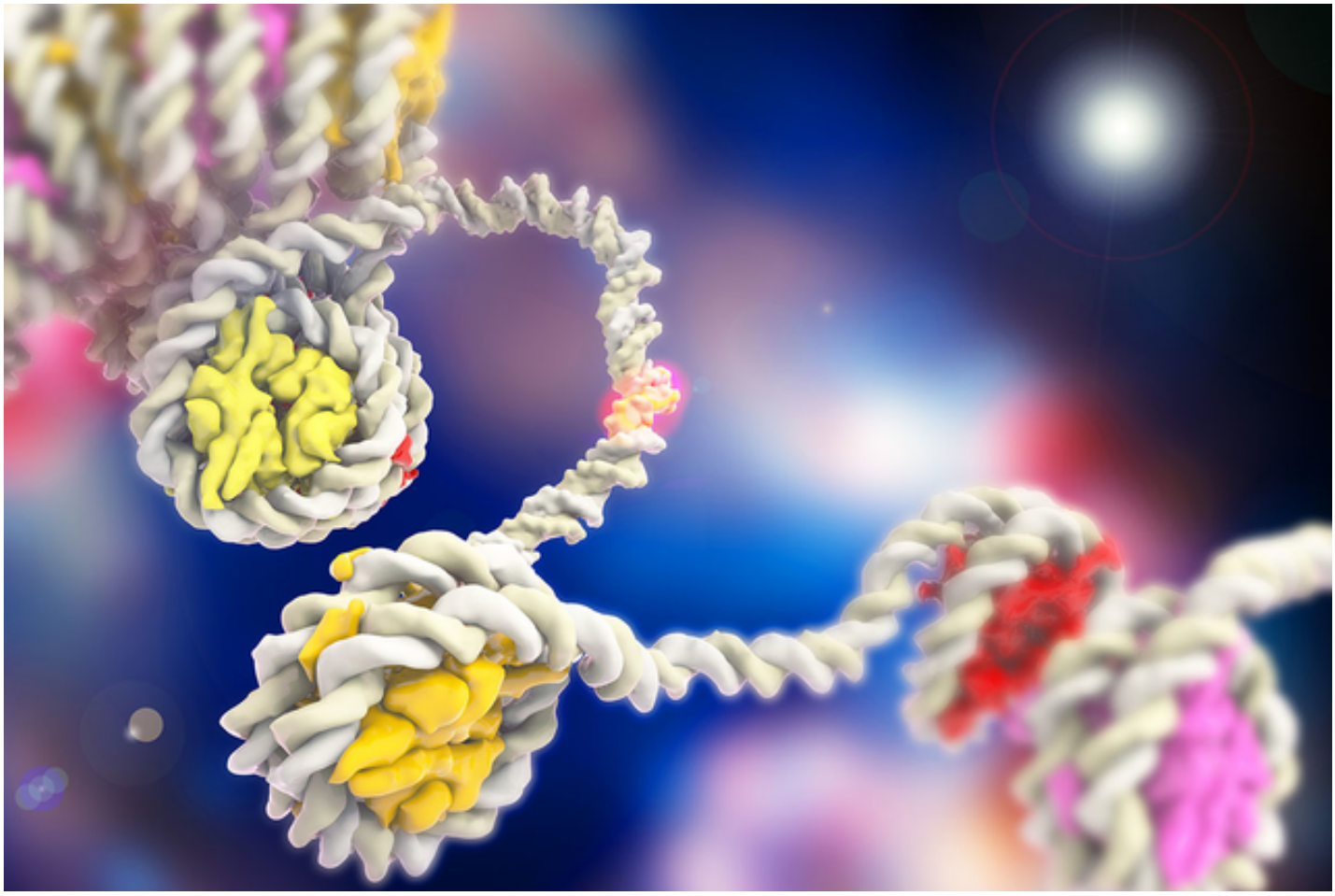
Research Clarifies How IDH Mutations Cause Cancer

By Julie Grisham, **Monday, July 1, 2019**



Inside the cell nucleus, DNA strands wrap around spool-like proteins called histones. How DNA is spooled can ultimately influence how and when genes get made into proteins.

Summary

MSK researchers have made new discoveries about how changes in a family of cancer-causing genes can lead to epigenetic changes.

A family of genes called IDH are associated with cancer. These genes make enzymes called isocitrate dehydrogenases. The enzymes help break down nutrients and generate energy for cells. Mutations in IDH genes prevent cells from differentiating, or specializing, into the kind of cells they are ultimately supposed to become.

When cells can't differentiate properly, they may begin to grow out of control. Scientists are still learning about what controls this process.

Now a team of researchers working in the lab of Memorial Sloan Kettering President and CEO **Craig Thompson** have made discoveries about how this malfunction occurs, at least in test tubes. Although the work is still in an early stage, they hope their findings will eventually contribute to new approaches for developing cancer drugs.

"Although IDH mutations are not very common overall, there are some diseases where these genetic changes contribute to a significant portion of cases," says **Juan-Manuel Schvartzman**, a postdoctoral fellow in the Thompson lab, an instructor in the Gastrointestinal Oncology Service, and the first author of a **paper** recently published in the *Proceedings of the National Academy of Sciences* (*PNAS*). "For these subtypes of cancer, better targeted therapies are needed."

IDH mutations are found in about one-quarter of people with **acute myeloid leukemia (AML)**, the most common type of leukemia in adults. They may also be found in a type of bile duct cancer called cholangiocarcinoma, a **bone cancer** called chondrosarcoma, low-grade glioma, and some kinds of lymphoma. The mutations occur much less frequently in more common cancers, such as colon cancer, breast cancer, and lung cancer.

> "One thing that's exciting [about this research] is the ability to understand more about how cells are wired."

Juan Manuel Schvartzman
physician-scientist

Deciphering Underlying Changes

To learn more about how IDH mutations block differentiation, the investigators studied them in the context of a well-characterized model: cells called fibroblasts that can be coaxed to become muscle cells. By figuring out how the mutations prevent muscle cells from forming properly, the team aimed to get at the underlying defects in cells that these mutations cause.

Earlier research showed that IDH mutations influence cells through epigenetic changes. **Epigenetics** involves changes in gene expression that do not cause changes in the DNA sequence. Many of these have to do with the way DNA is packaged in the nucleus of a cell. The strands are wrapped around spool-like proteins called histones. Small chemical groups attached to DNA and histones — including fragments called methyl groups — can affect how DNA is spooled. Ultimately, this can influence how and when genes get made into proteins.

Specifically, IDH mutations lead to the formation of a molecule called 2-hydroxyglutarate (2HG). This molecule, in turn, can block the removal of methyl groups.

In the *PNAS* paper, the investigators dove deeper into the specific epigenetic changes caused by IDH mutations. “What we found was that they didn’t have much to do with DNA methylation, which is what we previously thought,” Dr. Schvartzman says. “Instead, they were related to methylation on histones.”

This change affects how the DNA strands are wrapped around histones. When they are tightly wrapped, it can prevent certain regions of DNA from being accessible. This can affect which genes get made into proteins.

What Is Epigenetics, and Why Is Everyone Talking about It?

Epigenetics is frequently in the news, but there's lots of confusion about just what it entails.

Learn more

Expanding the Development of Drugs

There already are drugs that are approved to work in AML caused by IDH mutations. **Ivosidenib (Tibsovo®)** targets *IDH1*, and **enasidenib (Idhifa®)** targets *IDH2*. Both of these drugs prod cancer cells into differentiating normally. But investigators say that there are many more avenues to be explored for new drugs that work against IDH-mutant cancers.

"I'm very interested in looking not just at tumors that are IDH mutant but more broadly at how these cellular changes affect the ability of those cells to differentiate," Dr. Schvartzman says. "In addition to the buildup of 2HG, there are other changes in the cell that may prevent methyl groups from being removed from histones. We want to study those as well.

"It's a little early to talk about how this could be applied to new drugs," he concludes. "But one thing that's exciting is the ability to understand more about how cells are wired and how different cellular changes affect levels of methylation. There are many enzymes we can start to explore that could be interesting for new cancer drugs."

This research was funded by a National Institutes of Health/National Cancer Institute grant (P30CA008748) and a Hope Funds for Cancer Research postdoctoral fellowship.

Dr. Thompson is a founder of Agios Pharmaceuticals, which develops drugs that target IDH mutations, and a member of its scientific advisory board. He previously served on the board of directors of Merck and Charles River Laboratories.

Comments

> Commenting is disabled for this blog post.

Diana Downey

Jul 2, 2019 • 3:43 PM
I am in the UK and have cholangiocarcinoma and IDH1 and FGFR mutations. I have been on the Incyte trial which was partislly successful but now have metasisis to the spine. I amf looking for a promising IDH1 trial. Can you help me? Thanks

Memorial Sloan Kettering

Jul 3, 2019 • 9:14 AM
Dear Diana, we're sorry to hear about your diagnosis. If you'd like to arrange a consultation with our doctors in New York or a remote **records review**, you can contact our **International Center** at **international@mskcc.org** or 1-**212-639-4900**. Thank you for your comment and best wishes to you.

Danielle Munson

Jul 16, 2019 • 9:29 AM
I lost my son Chris to dedifferentiated chondrosarcoma after a short fight. He had 1DH1 mutation and was born with hereditary multiple exostoses. I would like to understand if my other son is has never had an issues and was never diagnosed with HME. Can he still carry this mutation. I also would like to help support these type of studies. No child or adult should go through this with no treatment options that help. Thanks

Memorial Sloan Kettering

Jul 16, 2019 • 1:31 PM
Dear Danielle, we are very sorry for the loss of your son, Chris. If you are interested in speaking with someone in our **Clinical Genetics Service** about the risk of a hereditary cancer-related gene in your family, you can call **646-888-4050**. If you are not in New York and not able to travel to New York for an appointment with our experts, we recommend that you seek out a genetic counselor at an academic