Something New Under the Sun: Study in Leukemia Finds Role for Helios Protein

By Julie Grisham, **Wednesday, November 21, 2018**

This illustration depicts Helios, the ancient Greek sun god for which the Helios protein is named, changing the packaging of DNA. Researchers have learned that the Helios protein regulates the winding and unwinding of DNA. Illustration by Olga Kharchenko

Summary

MSK researchers have found that Helios — a protein named after the Greek sun god — contributes to one type of leukemia when it's missing but can lead to the formation of a different leukemia type when it's present.

Proteins are one of the fundamental building blocks of life, controlling many of the vital functions carried out by cells. These activities include cell growth, division, and death. Sometimes the same protein can have more than one job, depending on how it interacts with other proteins in a cell.

The latest example of a protein with a dual role is one called Helios. When it's missing, Helios can contribute to a type of pediatric blood cancer called B-acute lymphoblastic leukemia (B-ALL). But researchers at Memorial Sloan Kettering are now learning that when Helios is abundant, it can actually drive the formation of a different and a more common type of blood cancer called **acute myeloid leukemia (AML)**. The findings were **published in *Cell Stem Cell***.

"There are not a lot of examples of this type of situation," says senior author **Michael Kharas**, a cancer biologist in the **Molecular Pharmacology Program** in the Sloan Kettering Institute. "Occasionally, there are proteins that have completely different activities in different kinds of cancer. In this study, we figured out the ways in which the protein works and showed how it turns different genes on and off."

A Protein That Regulates Genes

Helios is the name for the ancient Greek god of the sun. (Genes and proteins are sometimes given whimsical names, and Helios is a member of a family of proteins that are all named after characters from Greek mythology.) The Helios protein acts as an epigenetic regulator, which means it can control which genes get turned on and which genes get turned off. It exerts control by regulating chromatin, the part of the cell that packages DNA. If you imagine DNA as long strands of yarn, chromatin is the spool that the strands wrap around. When DNA is tightly wound, it's hard for proteins to get made because the machinery that's needed to start the process can't make contact with the DNA. But when it's unwound, the DNA becomes accessible.

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In the new study, investigators found that Helios unwraps DNA from chromatin in areas that are important for the survival of leukemia cells. It also winds up the DNA in locations that are important for blood stem cells to turn into specific cell types. This process is called differentiation.

In someone with AML, the bone marrow produces immature white blood cells called myeloblasts rather than healthy, normal blood cells. Myeloblasts are unable to function like normal blood cells. They grow out of control and crowd out healthy cells. High levels of Helios are present in leukemia stem cells, which are essential for leukemia to grow. These cells are also thought to be the cause for relapse.

“In the case of AML, Helios controls the program that leukemia stem cells use,” Dr. Kharas explains. “In some areas of the genome, it keeps the chromatin open, and in other places, it keeps the chromatin closed. The genes that are important for the cells’ ability to keep growing are left on, and those that would drive normal differentiation are turned off.”

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By contrast, in the pediatric blood cancer B-ALL, it’s the absence of Helios that causes trouble. Earlier research found that Helios was lost in about half of people with a type of B-ALL called hypodiploid B-ALL.

In this study, however, investigators found that knocking down, or deleting, Helios can reduce the number of leukemia stem cells. Furthermore, Helios is required for leukemia cells to survive, and when it’s removed, leukemia cells stop growing and differentiating, and ultimately die.

To confirm that Helios contributes to AML development, the investigators also transplanted human leukemia cells into mice models. They found that when Helios was deleted, the mice had a greater reduction in leukemia cells and lived longer.

What's Next? Targets for Drug Development

Based on the findings, the researchers hope to develop drugs that target Helios as a treatment for AML. Dr. Kharas doesn't believe there is any danger in causing B-ALL by blocking Helios, since several other mutations are needed to drive the formation of that cancer. In addition, the mice that had Helios blocked in their blood cells didn't show any signs of other cancers, including B-ALL, and had normal blood stem cell function. But until further research is conducted, investigators won't know for sure.

Dr. Kharas notes that other researchers have discovered that Helios plays a role in the proper functioning of a type of white blood cell that affects immune response. This suggests that drugs that influence Helios could also be used to boost immune therapies for cancer.

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