Splicing May Be an Effective Target in the Fight against Cancer

By Julie Grisham, **Wednesday, July 18, 2018**

Physician-scientist Omar Abdel-Wahab studies the process called splicing in his lab.

Summary

Research into how proteins are made is being used for a possible new treatment for blood cancers.

Cancer is a disease of the genes. But genes don't directly cause the uncontrolled cell growth that characterizes the disease — proteins produced by those genes do.

Consequently, most precision cancer drugs target these malfunctioning proteins and block their activity.

Some investigators are looking to stop cancer by blocking steps on the path from gene to protein. One of these tactics focuses on a process called splicing. It has yielded a drug, called H3B-8800, which is now being evaluated in an **early-stage clinical trial for myelodysplastic syndrome (MDS) and two types of leukemia**.

"This drug works differently than other targeted drugs that block proteins," says Memorial Sloan Kettering physician-scientist **Omar Abdel-Wahab**. "But we think it's a very good approach because between 60 and 80% of people with **MDS** have the defect in splicing that this drug targets."

A Promising New Focus for Cancer Drugs

Genes get translated into proteins through an intermediate molecule called messenger RNA (mRNA). If genes are the written instructions for how to make a protein, and the protein itself is the final product, then mRNA is the go-between that brings the plans to the construction crew. Splicing is one part of the manufacturing process. It determines which part of the genetic sequence gets used, and which part is cut out and thrown away. When splicing goes wrong, it can lead to defective proteins that drive cancer growth.

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Dr. Abdel-Wahab studies the splicing process **in his lab** in the **Human Oncology and Pathogenesis Program**. Based on a recent discovery that genetic changes in the splicing process are very common in **leukemias**, he found that cells carrying these genetic changes are especially sensitive to drugs.

Research on splicing and mRNA is part of the broader field called **epigenetics**. Epigenetics is the study of changes in cell behavior that are not due to changes in the DNA sequence. It's an increasingly important focus in cancer research. Dr. Abdel-Wahab is also a member of MSK's **Center for Epigenetics Research**, which focuses on studies into how epigenetic changes can cause cancer.

Finding a Way to Correct Genetic Splicing Errors

H3B-8800, which is being developed by a company called H3 Biomedicine, is a version of a **natural substance** that was first found in soil bacteria. It was chemically modified to work better as a drug. Earlier this year, Dr. Abdel-Wahab, along with MSK MDS expert **Virginia Klimek**, was part of an international team that reported on the function and efficacy of H3B-8800 in a dish and in mouse models of leukemia. The study, **published in *Nature Medicine***, found that H3B-8800 can induce cell death in cancer cells that are dependent on splicing.

"Mutations in splicing genes are very common in MDS, so we fully expect that these mutations are linked to the bone marrow dysfunction and low blood counts seen in MDS," Dr. Klimek explains. "The development of this new targeted drug is exciting because it has the potential to help many people with MDS. We're grateful for those who donated the blood and bone marrow samples that were used to make these discoveries, and which led to the development of H3B-8800."

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Virginia M. Klimek
medical oncologist

The drug is now being tested in a phase I clinical trial at MSK and several other hospitals to determine the highest dose that can be given safely and to look for side effects. At MSK, the trial is being led by Dr. Klimek.

"This effort really highlights the importance of collaboration between doctors and scientists," she adds. "Such collaborations enable us to take observations from patients into the research lab, where breakthrough discoveries can be made and turned into new treatments. Our collaborative approach and our tremendous research program are some of MSK's greatest strengths."

"Research in the lab has taught us a lot about how errors in splicing can impact the products of genes," Dr. Abdel-Wahab notes. "We think these functions are particularly important for different kinds of blood cells, but it's possible this approach may work for some solid tumors as well."

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