Researchers discover master regulator that drives majority of lymphoma

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A soon-to-be-tested class of drug inhibitors were predicted to help a limited number of patients with B-cell lymphomas with mutations affecting the EZH2 protein. However, a research team, led by investigators at Weill Cornell Medical College, now report that these agents may, in fact, help a much broader cross section of lymphoma patients.

The study, reported in *Cancer Cell*, found that the EZH2 protein the drug agents inhibited is a powerful regulatory molecule in B-cells, and a key driver of cancer in these immune cells.

The study's lead investigator, Weill Cornell Medical College's Dr. Ari Melnick, suggests that combining an EZH2 inhibitor with another related targeted therapy may offer a much improved treatment for follicular lymphoma, a cancer that currently has no cure, as well as a non-toxic alternative to chemotherapy for at least a third of diffuse large B-cell lymphomas. Because these two lymphomas account for 70 percent of adult lymphomas, Dr. Melnick believes the new therapy could potentially help a broad cross section of lymphoma patients.

"Our research indicates that these inhibitors will be remarkably effective. I am very optimistic," says Dr. Melnick, the Gebroe Professor of Hematology/Oncology, professor of medicine and director of the Raymond and Beverly Sackler Center for Biomedical and Physical Sciences at Weill Cornell. "Researchers had thought EZH2 inhibitors would only help patients with a mutation in their EZH2 gene, which

represents a small subset of lymphoma patients. What we found is that a majority of lymphomas turn out to be dependent on normal EZH2, not just mutated EZH2."

Tumor Cells Depend on the EZH2 Master Regulator

The new study was aimed at understanding what normal as well as mutated EZH2 does within B-cells—basic information that remained unknown despite more than a decade of research into the protein.

The role of B-cells (white blood cells known as B-lymphocytes) is to produce antibodies against invading microbes. What the researchers discovered is that EZH2 is required in order for the immune system to generate germinal center B-cells, which are the cells that make the most powerful type of antibodies.

Germinal center B-cells divide extremely quickly and try to create within them the high affinity antibodies that will be beneficial to fight off invading infections. This process happens constantly because of our exposure to microorganisms.

"Most B-cell lymphomas arise from germinal center B-cells—germinal centers are the engine for formation of lymphomas," says Dr. Melnick. "The reason for this is because germinal center B-cells divide very, very quickly while at the same time mutating their antibody genes. Unfortunately, many other genes get mutated when this happens, which can eventually result in lymphoma formation."

It turns out that the behavior of germinal center B-cell is orchestrated by EZH2, Dr. Melnick discovered. "EZH2 is a master regulator protein that turns off the brakes that prevent cell division, so it allows cells to divide without stopping," he says.

EZH2 also has a second function, which Dr. Melnick calls "surprising and perhaps even more important.

"It prevents germinal cells from transitioning to antibody-secreting cells," he says. "Indeed, in the normal immune system EZH2 prevents B-cells from exiting germinal centers so that these cells can continue to undergo sustained rapid cell division, which continues until the immune system says to stop. Then EZH2 goes away, and B-cells can develop into antibody-secreting cells, which send antibodies into the circulation to fight off infection."

Interestingly, mutations of EZH2 cause it to be even more efficient at promoting germinal center B-cell division and permanently keep them locked in this behavior, Dr. Melnick says. But he adds that most lymphomas that are derived from germinal cell B-cells are dependent on EZH2, whether normal or mutated, to sustain growth.

"Germinal center cells absolutely require EZH2 and the lymphomas that arise from germinal center cells inherit that need regardless of whether they have mutations," Dr. Melnick says. "We discovered that it is not just the small percentage of patients with EZH2 mutations who are candidates for these inhibitors. It is actually most of the lymphomas that originate from germinal center B-cells—and that represents the majority of patients."

The researchers report the development of a novel and highly specific EZH2 inhibitor, tested its effects against large panels of lymphoma cells and found that it works particularly well against germinal center-derived lymphomas regardless of whether or not they have EZH2 mutations.

"The case of EZH2 exemplifies a critically important emerging concept in cancer—that tumor cells are dependent on the master regulators that are required to sustain the normal cell type from which they originate,"

Dr. Melnick adds.

According to researchers, another implication of the study is that it may be possible to combine an EZH2 inhibitor with a drug that targets BCL2, which is also in clinical testing, to achieve a more powerful synergistic effect.

"EZH2 and BCL2 mutations tend to occur together in germinal center derived lymphomas. In our report, we show that indeed these two genes cooperate to drive lymphoma formation from germinal center B-cells, and so a combination therapy that inhibits both genes might offer a very powerful therapy," says Dr. Melnick. "Indeed, combining EZH2 inhibitors and BCL2 inhibitors had a much greater effect in cells and in animal models of lymphomas than either drug alone." These results pave the way for translation of combinatorial-targeted therapy for patients with incurable lymphomas.

Provided by Weill Cornell Medical College