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Researchers find Achilles' heel of acute lymphoblastic leukemia

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Researchers at The Ottawa Hospital and the University of Ottawa have found the Achilles' heel of one of the most aggressive forms of leukemia that affects both children and adults. They have also identified a possible new treatment that exploits this fatal weakness.

Their study, published in *Genes & Development* on March 1, 2016, focuses on a type of acute lymphoblastic leukemia (ALL) that involves a gene called TAL-1. Senior author Dr. Marjorie Brand and her team discovered that a compound called GSK-J4 can kill this form of cancer.

By transplanting cancer cells from human patients into normal mice, the authors showed that the compound can kill the leukemia quickly, efficiently, and with no short-term side effects. GSK-J4 was created by the pharmaceutical industry for research purposes, and has never been used as a cancer therapy.

"It's very exciting because this is the first time anyone has found a potential personalized treatment for this aggressive disease," said Dr. Brand, a senior scientist at The Ottawa Hospital and professor at the University of Ottawa. "Unlike current therapies, ours targets the offending gene without harming the rest of the body."

Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children. It develops in the white blood cells that usually help the body fight infection. The type of cancer Dr. Brand studies is called T-ALL, because it affects a particular kind of white blood cells called T-cells. T-ALL represents 15 percent of childhood ALL cases. This study in particular dealt with a common form of T-ALL called TAL-1.

Today the treatment is the same for all forms of T-ALL: harsh chemotherapy with side-effects including risk of secondary cancers later in life and stunted growth in children. If the cancer returns after treatment, patients usually die soon after.

"With the current treatments, you get a 90 percent cure rate in some of the T-ALL subtypes," said lead author Dr. Aissa Benyoucef, a postdoctoral Fellow at The Ottawa Hospital and the University of Ottawa. "But in the TAL-1 subtype that we're studying, you get only a 50 percent cure rate. It's very aggressive."

Dr. Marjorie Brand and her team decided the best way to find a better treatment for the TAL-1 subtype was to investigate exactly how it works at a molecular level.

The team looked at the TAL-1 gene, which in certain circumstances can transform the cells that will become T-cells into cancer cells. TAL-1 does this by activating genes that make white blood cells grow uncontrollably. Eventually these cancerous cells spread throughout the blood and body, causing leukemia.

The research team discovered that TAL-1 has a weak spot: It needs a partner in crime, an enzyme called UTX, to trigger cancer production. So when Dr. Brand's team used a compound called GSK-J4 to turn off UTX, it completely stopped the growth of TAL-1 type cancer cells. This treatment specifically worked only for TAL-1 subtype, and not any other types of T-ALL.

The team tested these findings in mouse models injected with cells from human TAL-1 type leukemia. After treating the mice with GSK-J4 over three weeks, the researchers found the number of cancer cells in their bone marrow decreased by 80 percent. In addition, the compound left non-cancer cells unharmed, and had no short-term effects on other organs of the body.

"While our study is a proof of concept, these promising results might one day lead to a similar targeted treatment for humans," said second author of the study Dr. Carmen Palii, a research associate in Dr. Brand's lab.

In the meantime, the research team is conducting pre-clinical studies in mouse models, looking at the effects of increased doses as well as long-term side effects of GSK-J4.

"Learning how a disease works at a molecular level needs to happen before any kind of successful drug can be developed," said Dr. Brand. "You need to do laboratory studies to find the right treatment and prove it works."

Source:

Ottawa Hospital Research Institute
