New cancer target for non-Hodgkin's lymphoma

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Physician-scientists from Weill Cornell Medical College have discovered a molecular mechanism that may prove to be a powerful target for the treatment of non-Hodgkin's lymphoma, a type of cancer that affects lymphocytes, or white blood cells. By exploiting this mechanism, researchers have been able to powerfully suppress tumor formation in lab testing and in animal models.

Promising results have led to the design of a clinical trial that will soon be under way to test a compound -- called PU-H71 -- in human patients. This compound is in a new class of drugs, called heat shock protein inhibitors.

Standard treatment for non-Hodgkin's lymphoma includes radiation therapy, chemotherapy and monoclonal antibodies. Approximately 66,000 people are diagnosed in the United States each year and approximately 50 percent of patients will not be cured by current treatments.

The author's results are published online today in the prestigious journal *Nature Medicine*.

"We observed almost complete tumor regression after treating the animals with PU-H71," says Dr. Ari Melnick, associate professor of medicine from the Raymond and Beverly Sackler Center for Biomedical and Physical Sciences at Weill Cornell Medical College. "I hope that clinical testing will have similar results for human participants."

The research team discovered that a molecule called heat shock protein 90 (Hsp90) is necessary for the functioning of a protein called BCL-6, which is known to drive the activity of lymphoma tumor cells.

BCL-6 is the most commonly involved protein in diffuse large B-cell lymphomas, which is the most common form of non-Hodgkin's lymphoma. Approximately 70 percent of these tumors test positive for BCL-6, making it a primary target for therapies.

Dr. Melnick and his team found that Hsp90 and BCL-6 joined together within cancer cells to form a complex. They also learned that Hsp90 binds directly to the gene responsible for producing the BCL-6 protein, which led them to believe that blocking Hsp90 would have a powerful effect on BCL-6 production within the cell and, therefore, tumor formation.

To prevent the two molecules from joining, the scientists tested the experimental drug, PU-H71, which was designed to block the activity of Hsp90. PU-H71 was developed by Dr. Gabriela Chiosis, a principal author of the study, from the Memorial Sloan-Kettering Cancer Center, in New York City. The scientific team discovered that exposing lymphoma cells to PU-H71 in laboratory experiments prevented the combination of the two molecules -- killing lymphoma cells and inhibiting new cell reproduction.

"The next step was to test the findings in an animal model to see what kind of effect PU-H71 had," explains Dr. Melnick. "We were excited to find that the treated animals' tumors decreased in both size and weight, and that the animals had a significantly prolonged survival compared with controls."

The researchers also found that PU-H71 had a very low toxicity in the animal models. Dr. Melnick believes that this may indicate that when

tested in human patients, the drug will be well tolerated, with few side effects, such as damage to the bone marrow and immune system, which are common in cancer therapies.

Source: New York- Presbyterian Hospital (news : web)