Researchers highlight new direction for drug discovery

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In a discovery that rebuffs conventional scientific thinking, researchers at Georgetown University Medical Center (GUMC) have discovered a novel way to block the activity of the fusion protein responsible for Ewing's sarcoma, a rare cancer found in children and young adults.

In the paper published online July 5 in Nature Medicine, they report discovering and successfully testing a small molecule that keeps the fusion protein from sticking to another protein that is critical for tumor formation. The researchers say this interaction is unique - and is especially surprising since the Ewing's sarcoma fusion protein is extremely flexible, which allows it to change shape constantly.

"Most targeted small molecule cancer drugs inhibit the intrinsic activity of a single protein, but our agent stops two proteins from interacting. This has never been shown before with a cancer-causing fusion protein and represents a potentially novel medical therapy in the future," says the study's lead investigator, Jeffrey Toretsky, MD, a pediatric oncology physician and researcher at GUMC's Lombardi Comprehensive Cancer Center.

The study could provide a model upon which to design treatment for other disorders caused by the interaction between two proteins, and may be especially useful in cancers caused by translocations of genes, such as sarcomas and leukemias, the researchers say. Agents in use now that work against fusion proteins inhibit a single protein to stop intrinsic enzymatic activity; one example is Gleevec, used for chronic

myelogenous leukemia (CML). The Ewing's sarcoma fusion protein, known as EWS-FLI1, lacks enzymatic activity, "and this difference is why our work is significant," Toretsky says.

In the United States, about 500 patients annually are diagnosed with the cancer, and they are treated with a combination of five different chemotherapy drugs. Between 60-70 percent of patients survive over time, but with side effects from the treatment. Few additional treatment options are available for patients whose cancer progresses, Toretsky says.

Ewing's sarcoma is caused by the exchange of DNA between two chromosomes, a process known as a translocation. The new EWS-FLI1 gene is created when the EWS gene on chromosome 22 fuses to the FLI1 gene on chromosome 11, and its product is the fusion protein responsible for cancer formation. It is a so-called disordered protein, which means it does not have a rigid structure. A number of cancer-causing proteins are disordered.

In their 15-year search for a new treatment for Ewing's sarcoma, Toretsky and his colleagues were the first to make a recombinant EWS-FLI1 fusion protein. They used it to discover that the fusion protein stuck to another protein, RNA helicase A (RHA), a molecule that forms protein complexes in order to control gene transcription. "We believe that when RHA binds to EWS-FLI1, the combination becomes more powerful at turning genes on and off," says the study's first author, Hayriye Verda Erkizan, PhD, a postdoctoral researcher in Toretsky's lab.

Then, from a library of 3,000 small molecules loaned to Georgetown from the National Cancer Institute, the researchers searched for a small molecule that would bind on to EWS-FLI1. They found one, and further discovered the same molecule, NSC635437, could stop EWS-FLI1's fusion protein from sticking to RHA.

This was a wonderful discovery, Erkizan says, because the notion long accepted among scientists is that it is not possible to block protein-protein interactions given that the surface of many of these proteins are slippery - much too flexible for a drug to bind to.

They tested the agent in laboratory cell culture, and with the help of GUMC's Drug Discovery Program, the researchers designed a stronger derivative compound they called YK-4-279. In this study, they tested YK-4-279 in two different animal models of Ewing's sarcoma and found that the agent significantly inhibited the growth of tumors. There was an 80% reduction in the growth of treated tumors compared to untreated tumors.

Toretsky says that while the agent needs to be "optimized," these results serve as a proof of principle that inhibiting protein-protein interaction can work as a novel therapeutic that will target only cancer cells.

"We may be able to use this strategy to attack proteins we thought to be impervious to manipulation," he says.

Source: Georgetown University Medical Center (news : web)