New drug blocks gene driving cancer growth

September 14 2014

In *Nature*, Dan Theodorescu, MD, PhD, director of the University of Colorado Cancer Center describes a new drug, representative of a class of new drugs, that is active against a major driver of cancer metastasis. Credit: CU Cancer Center

When active, the protein called Ral can drive tumor growth and metastasis in several human cancers including pancreatic, prostate, lung, colon and bladder. Unfortunately, drugs that block its activity are not available.

A study published today in the journal *Nature* uses a novel approach to target the activation of these Ral proteins: "When you want to keep an alligator from biting you, you can tie its mouth shut. We took another

approach – we put a stick in its mouth to hold it open," says Dan Theodorescu, MD, PhD, professor of Urology and Pharmacology, director of the University of Colorado Cancer Center and the study's senior author, who led a multidisciplinary team of investigators from the University of Colorado, Indiana University, the University of Virginia and Yale University.

The study used sophisticated computer models to examine the structure of the Ral protein in its "inactive" form, looking specifically for changes in this structure as the protein became "active". It turned out that "inactive" Ral has a cavity that disappears when the protein becomes active. This was the "mouth" and now Theodorescu and colleagues needed the "stick".

The search for the stick required using a computer to dock 500,000 compounds in this cavity, which resulted in 88 candidate small molecules that might bind to inactive Ral and prevent its activation. The researchers took the findings to human cancer cells, treating these with the compounds to see which resulted in the greatest reduction of Ral activation. A handful of compounds emerged from the group as especially able to reduce Ral activation in lung cancer cells.

Further testing evaluated the compounds' abilities to slow the growth of human cancer cells in suspension – a proxy for metastasis. One molecule, RBC8 proved most successful in this regard. To further refine the working molecule, the team synthesized derivatives of RBC8 and compared these derivatives to the parent molecule, finding that a compound they labeled BQU57 was quite effective.

Next, tests moved to human lung cancer cell models in mice, with the major question being whether cells in an animal model would take up BQU57 in a way that allowed the compound to eventually be a potential drug in cancer patients. In other words, would what worked in a dish also

work in an animal?

Sure enough, hours after dosing, BQU57 had entered tumor tissue. Not only had it entered tumor tissue, but the drug slowed the growth of these tumors. Analysis showed that BQU57 had stopped the activation of Ral in treated tumors.

"We still need to optimize these compounds and then characterize these agents for toxicity in several animal species and determine their optimal route of delivery, such as oral or intravenous before moving to the clinic," Theodorescu says. "But we see this work as a valuable first step in the development of a novel class of therapeutic agents directed at Ral. The concept of targeting sites on proteins that collapse upon activation, and whose collapse is required for activation, could in principle be used to discover drugs aimed at other proteins driving human disease as well."

More information: Discovery and characterization of small molecules that target the GTPase Ral, *Nature*, DOI: 10.1038/nature13713

Provided by University of Colorado Denver