MedicalXpress

Researchers identify new mechanism to target 'undruggable' cancer gene

April 21 2016

RAS genes are mutated in more than 30 percent of human cancers and represent one of the most sought-after cancer targets for drug developers. However, this goal has been elusive because of the absence of any drug-binding pockets in the mutant RAS protein. A new study published in the April 20 issue of the journal *Cell* by researchers at the Icahn School of Medicine at Mount Sinai led by E. Premkumar Reddy, PhD, has identified a new mechanism for targeting this important cancer gene.

Mutations in RAS genes (HRAS, KRAS and NRAS) are frequently observed in many of the most common and lethal tumors, including cancers of the pancreas, lung and colon. Although molecular oncologists have made significant headway in understanding these mutations and their impact on cellular signaling, little progress has been made towards developing drugs that systematically target the RAS oncogenes. This lack of progress has led many in the field to label RAS an "undruggable" cancer gene.

Dr. Reddy and a team of scientists from the Icahn School of Medicine, The Scripps Cancer Research Institute, Albert Einstein College of Medicine, and the New York Structural Biology Center have identified the first small molecule able to simultaneously inhibit the different signaling pathways activated by RAS oncogenes. This small molecule, also called rigosertib or ON01910.Na, acts as a protein-protein interaction inhibitor that prevents binding between RAS and signaling proteins (including RAF, PI3K and others) that turn a cell into a cancer

cell. The multi-disciplinary team performed structural experiments to confirm the mode of action for rigosertib and also demonstrated the potential for this targeted mechanism in the treatment of several RAS-driven cancers.

"This discovery is a significant breakthrough for the cancer field," said Dr. Reddy, a Professor of Oncological Sciences at the Icahn School of Medicine at Mount Sinai. "Rigosertib's mechanism of action represents a new paradigm for attacking the intractable RAS oncogenes. Our current focus is to use the information from our studies with rigosertib to design the next generation of small molecule RAS-targeting therapies, and we are excited to have recently identified several compounds which we think improve on the qualities of rigosertib."

This drug is currently in Phase III clinical trials for the treatment of myelodysplastic syndrome (MDS) at multiple sites including Mount Sinai.

Provided by The Mount Sinai Hospital