New idea for targeting the common cancer protein KRAS

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Patients with cancers driven by the protein KRAS, which are particularly hard to treat, may benefit from small molecules that attach to and disrupt the function of a KRAS-containing protein complex, according to results presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Oct. 19-23.

Mutant forms of the protein KRAS are found in approximately 30 percent of all cancers. They are responsible for many of the hallmarks of these cancers, and KRAS is, therefore, considered an important therapeutic target. However, attempts to develop clinically useful KRAS-targeted drugs have been unsuccessful.

"KRAS is a molecular switch," said Michael Burns, a doctor of medicine and doctor of philosophy candidate at Vanderbilt School of Medicine in Nashville, Tenn. "In the 'on' state it transmits signals that drive cell growth and survival. In many cancers, KRAS is permanently in the on state, and it is a highly validated therapeutic target.

"KRAS switches from off to on most efficiently when it is attached to a protein called SOS," explained Burns. "Each SOS protein attaches to two KRAS proteins, and we have identified a number of small molecules that bind to a particular part of SOS when it is in a complex with two KRAS proteins. These small molecules disrupt the function of the complex, ultimately causing inhibition of the signaling pathways downstream of KRAS that drive cell growth and survival. Although our data were generated in biochemical assays and cell lines, they suggest a potential

way to therapeutically target KRAS, which has not been possible to date."

KRAS switches from off to on during a process called guanine nucleotide exchange, and SOS increases the rate at which this process occurs. Burns and colleagues hypothesized that small molecules that blocked SOS-mediated guanine nucleotide exchange would prevent KRAS switching on and, therefore, inhibit the signaling pathways downstream of KRAS that drive cell growth and survival.

Instead, they found that a number of small molecules that attached to a special pocket in a region of SOS called the CDC25 domain and increased SOS-mediated guanine nucleotide exchange actually inhibited two of the major signaling pathways downstream of KRAS: the MAPK and PI3K signaling pathways.

The researchers are actively investigating why small molecules that increased SOS-mediated guanine nucleotide exchange in biochemical assays blocked signaling downstream of KRAS in cell lines. They are also working to optimize the small molecules before they conduct studies in preclinical models of cancer.

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Title: Approach for targeting Ras with small molecules that activate SOS-mediated nucleotide exchange

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Aberrant activation of the small GTPase Ras by oncogenic mutation or constitutively active receptor tyrosine kinases (RTKs) results in the deregulation of cellular signals governing growth and survival in cancer. The guanine nucleotide exchange factor Son of Sevenless (SOS) catalyzes the rate-limiting step in the activation of Ras by exchanging GDP for GTP. SOS is therefore a key control point for the propagation of RTK and Ras signaling. Here we report the discovery of small molecules that bind to a unique pocket on the Ras:SOS:Ras complex, increase SOScat-catalyzed nucleotide exchange, and perturb Ras signaling pathways in cells. X-ray crystallographic studies of Ras:SOS:Ras complexed with these small molecules reveal that they bind in a hydrophobic pocket in the CDC25 domain of SOS adjacent to the Switch II region of Ras. The structure-activity relationships exhibited by these compounds can be rationalized on the basis of the x-ray structures of multiple co-complexes. In addition, structure-based mutational analyses indicate that this newly identified pocket is essential for compound activity. As predicted, these molecules increase Ras-GTP levels in cells. However, they unexpectedly inhibit MAPK and PI3K signaling. Our studies suggest a novel way to target K-Ras and offer possible starting points for the discovery of compounds that could be used to treat Ras-driven tumors.

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