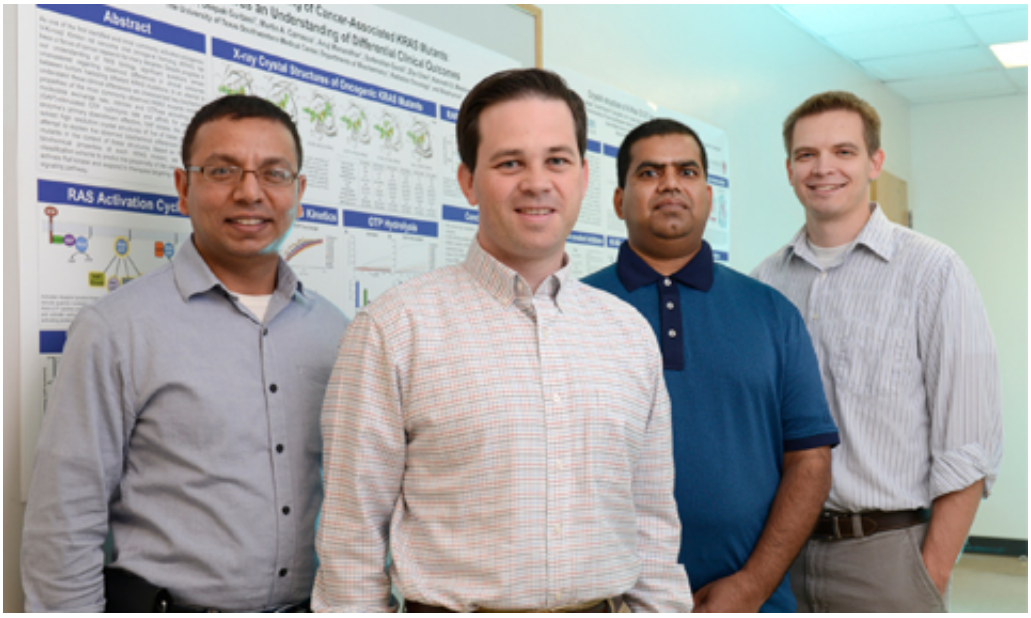
Team develops classification model for cancers caused by most frequently mutated gene in cancer

October 7 2015



(Left to right) Dr. Deepak Gurbani, Dr. Ken Westover, Dr. Sudershan Gondi, and Dr. John C. Hunter. Not pictured is Anuj Manandhar, who was also part of the team that developed a classification for cancers caused by KRAS, the most frequently mutated gene in cancer. Credit: UT Southwestern

UT Southwestern Medical Center researchers have developed a classification for cancers caused by KRAS, the most frequently mutated gene in cancer, that could eventually help oncologists choose more effective, customized cancer therapies.

That new strategy is based on models that researchers developed to classify cancers caused by *KRAS* (Kirsten rat sarcoma viral oncogene homolog) mutations, which cause cells to grow uncontrollably. Although *KRAS*-driven cancer mutations have long been a focus of cancer research , effective targeted therapies are not available.

"This work further supports the idea that not all oncogenic *KRAS* mutations function in the same way to cause cancer. The model we developed may help in subclassifying *KRAS*-mutant cancers so they can be treated more effectively, using therapies that are tailored to each mutation," said Dr. Kenneth Westover, Assistant Professor of Radiation Oncology and Biochemistry. "Furthermore, this study gives new fundamental understanding to why certain *KRAS*-mutant cancers, for example those containing the *KRAS* G13D mutation, behave as they do."

The findings are available in *Molecular Cancer Research*, a journal of the American Association for Cancer Research.

KRAS is one of the main members of the *RAS* family. About a third of all human cancers, including a high percentage of pancreatic, lung, and colorectal cancers, are driven by mutations in *RAS* genes, which also make cells resistant to some available cancer therapies, according to the National Cancer Institute.

Specific *KRAS* mutations dominate in particular cancer types, giving rise to the notion that certain *KRAS* mutations may have distinct biological activities. Laboratory and clinical data support this hypothesis.

In this study, the researchers evaluated eight of the most common *KRAS* mutants for key biochemical properties including nucleotide exchange rates, enzymatic activity, and binding activity related to a key signaling protein, RAF kinase. The researchers observed significant differences between the mutants, including about a tenfold increase in the rate of

nucleotide exchange for the specific mutant *KRAS* G13D, highly variable *KRAS* enzymatic activities, and variability in affinity for RAF. They also determined high-resolution, three-dimensional X-ray crystal structures for several of the most common mutants, which led to a better understanding of some of the biochemical activities observed.

"We attempted to use the observed structural changes to explain these differences in biochemical behavior. By integrating our data, we have proposed a biochemical classification scheme to predict the propensity of different *KRAS* mutants to signal through RAF kinase. If validated, our model could have value for selecting targeted therapies for cancer patients with specific *KRAS* mutations," said Dr. Westover.

Members of the Westover lab plan to continue this line of work by testing their models in more complex experimental systems, such as genetically engineered cancer cell lines.

Provided by UT Southwestern Medical Center

Citation: Team develops classification model for cancers caused by most frequently mutated gene in cancer (2015, October 7) retrieved 26 April 2024 from https://medicalxpress.com/news/2015-10-team-classification-cancers-frequently-mutated.html