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KRAS as a Target

BY HEATHER L. VAN EPPS, PHD

When it comes to KRAS activating mutations, colorectal cancer patients are not alone. These mutations are detected in up to one-fourth of all human cancers, particularly pancreatic, thyroid, lung, and colorectal. In pancreatic cancer, which afflicts more than 30,000 people in the United States each year and has a five-year survival rate of only 5 percent, virtually all tumors express mutated KRAS.

The impact of KRAS mutations on a patient's response to an EGFR-inhibiting drug is most clear in colorectal and lung cancers. Similar to colorectal cancer patients treated with Erbitux (cetuximab) or Vectibix (panitumumab), KRAS mutations may partly explain the reported failure of the EGFR inhibitors Iressa (gefitinib) and Tarceva (erlotinib) to benefit some lung cancer patients when given in combination with chemotherapy. Certain EGFR mutations, which occur in up to 35 percent of lung cancer patients, have been associated with a better response to Iressa and Tarceva, but this benefit is restricted to those with wild-type (normal) KRAS. The effect of KRAS status on Erbitux response in lung cancer is not yet clear.

Researchers have tried to use targeted drugs to block KRAS itself, but so far these drugs have been disappointing. The biology of the KRAS protein may help explain why.

The KRAS protein is activated by signals from cell surface growth receptors such as EGFR and is equipped with an internal on-off switch. Normally, KRAS controls its own activity by flipping the off switch, stopping further growth-promoting signals. Certain "activating" mutations in KRAS, which are confined to a few areas of the protein in all cancers, keep the switch stuck in the "on" position. Designing drugs to repair this defective switch is a much trickier prospect than, for example, designing those that block a protein's activity. Also, other proteins in the RAS family such as NRAS and HRAS can harbor activation alterations, so targeting KRAS alone may not always work.

The difficulty in targeting KRAS led researchers to focus on developing drugs that inhibit proteins downstream of KRAS. This approach is complicated, however, by the large number of cellular pathways that KRAS feeds into, making it difficult to know which pathway or pathways to cut off in order to cripple the cancer. To complicate matters further, drugs that block KRAS-dependent pathways could be toxic, as healthy cells also depend on KRAS for normal cell -functions.

The ultimate success of targeted molecules may lie in using specific combinations of drugs, which will depend on the molecular characteristics of each patient's

tumor.