Biomarkers discovered that may help predict response to drugs targeting KRAS-mutated NSCLC

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Scientists have identified biomarkers that may help predict whether patients with KRAS-mutated non-small cell lung cancer (NSCLC) will respond to concurrent treatment with an MEK inhibitor and a PI3 kinase inhibitor, a drug combination currently being investigated in ongoing clinical trials. The discovery was made as part of a study presented at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10, by Aaron N. Hata, M.D., Ph.D., a clinical fellow at the Massachusetts General Hospital in Boston.

Although several targeted therapies have been developed for patients with NSCLC, there are currently no proven targeted treatments for patients with NSCLC that harbors a KRAS mutation, which accounts for 20 percent to 25 percent of all NSCLC cases.

"Treatment with an MEK inhibitor and PI3 kinase inhibitor is a combination targeted therapy that may be effective for some patients with KRAS-mutant NSCLC, but it is not likely to be effective for all patients with this form of cancer," said Hata. "We want to be able to know which patients are going to respond to this combination therapy so that we can identify them and tailor their treatment accordingly."

To explore response to MEK and PI3 kinase inhibitors, Hata and colleagues studied a variety of NSCLC cell lines that all had mutated KRAS. They found that some of the cancer cell lines responded to the

drug combination by undergoing a process of cell death called apoptosis, whereas others did not.

"Our results were not surprising from the standpoint that induction of cell death is known to be important for response of cancer cells to therapy," Hata said. "What was surprising was the difference in apoptosis among the cell lines."

Specifically, lack of a cell death response to the combination of MEK and PI3 kinase inhibitors correlated with the decreased expression of pro-cell death mediators and the upregulation of anti-cell death regulators.

"We found that three specific proteins predicted response," Hata said. "Two of them, the BIM and PUMA proteins, induced cell death, and the third, the BCL-XL protein, inhibited cell death."

In addition, prior research has shown that many KRAS-mutant lung cancers also have a mutation in the TP53 gene, and the protein that it generates, P53, is known to be involved in the cell death process. In this study, the researchers found that TP53 mutation status did not predict response to the MEK/PI3 kinase inhibitor combination, but it did affect how the cells underwent cell death.

"Our research so far has focused on human cancer cell lines," Hata said. "We do not yet know if these correlations will hold true in patients."

Ideally, Hata and his colleagues would like to determine whether the proteins they identified are predictive of patient response to MEK/PI3 kinase inhibitors in the clinic.

"The ultimate goal would be having the ability to measure levels of these proteins in patients before they go on treatment," Hata said. "If they have favorable levels, that would tell us they are likely to respond to this

treatment, and if they do not, it would be better to select a different treatment."

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