Preclinical study indicates potential for novel inhibitor to overcome drug resistance induced by RAF, MEK inhibitors

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A new class of investigational medicines may help to treat patients with cancers driven by mutations in genes such as BRAF or KRAS/NRAS, including those patients who have become resistant to therapies that target BRAF directly, according to preclinical data presented at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10.

These new drugs, which are being developed by Merck, target ERK proteins. ERK proteins are components of the MAPK signaling pathway. In this pathway, they function downstream of RAS, BRAF and MEK. Inhibitors of BRAF and MEK have shown clinical efficacy in patients with melanoma harboring BRAF gene mutations.

"The MAPK pathway has been the subject of intense research to develop inhibitors against components of the pathway for the treatment of cancer ," said Ahmed Samatar, Ph.D., team leader of discovery oncology at Merck Research Laboratories. "Unfortunately, tumor responses are often transient and resistance to therapy is commonly associated with pathway reactivation involving the downstream module ERK1/2."

Samatar and colleagues hypothesized that inhibiting ERK in tumor cells driven by an activated MAPK pathway, as a result of either BRAF or RAS mutations, could provide a means of inhibiting tumor cell growth. The researchers used SCH772984, a novel ERK inhibitor, to test this theory.

Their results indicated that SCH772984 was a potent inhibitor of ERK1/2 in cultured human tumor cells with mutations in BRAF, NRAS or KRAS. The drug also induced tumor regression when tested in mouse models.

In addition, SCH772984 inhibited MAPK signaling and cell proliferation in human tumor cells resistant to BRAF and MEK inhibitors alone or in combination.

"Patients with cancer treated with BRAF and/or MEK inhibitors are susceptible to the development of resistance primarily via reactivation of ERK," Samatar said. "ERK inhibitors may provide a means to treat patients with these drug-resistant tumors, and an ERK inhibitor in combination with a BRAF or MEK inhibitor may also provide a strategy to overcome drug resistance."

Samatar and colleagues have initiated a phase I clinical trial of an investigational ERK inhibitor in patients with solid tumors.

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