New biomarker may help guide treatment of melanoma patients

October 22 2013

A functional biomarker that can predict whether BRAF-mutant melanomas respond to drugs targeting BRAF could help guide the treatment of patients with these cancers, according to results presented here at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Oct. 19 – 23.

Approximately 50 percent of melanomas harbor mutations in the BRAF gene, and the U.S. Food and Drug Administration has approved two drugs that target BRAF for the treatment of such cancers. However, not all patients with BRAF-mutant melanomas respond to treatment with these, and most of those patients who initially respond eventually relapse because their tumors become resistant to the effects of the BRAF-targeted drugs.

"Our study has identified decreased phosphorylation of the protein S6 after treatment with BRAF-targeted drugs as a functional biomarker that predicts sensitivity of BRAF-mutant melanomas to these drugs," said Ryan B. Corcoran, M.D., Ph.D., a Damon Runyon clinical investigator and assistant professor at the Massachusetts General Hospital Cancer Center and Harvard Medical School in Boston, Mass. "Importantly, we have developed a minimally invasive way to rapidly monitor post-treatment changes in S6 phosphorylation in patients' tumor cells. As a result, we think that we can quickly determine whether or not a patient is likely to respond to a BRAF-targeted drug and help speed up treatment decisions, although we need to verify this in larger clinical studies."

BRAF gene mutations lead to inappropriate BRAF protein activity, which, in turn, causes a cascade of inappropriate activation of numerous other proteins in the tumor cell. Corcoran and colleagues therefore examined whether there were differences in the activity of the proteins downstream of BRAF in BRAF-mutant melanoma cell lines responsive and resistant to the BRAF-targeted drug vemurafenib.

They found that decreased phosphorylation of the protein S6 after treatment with vemurafenib was associated with responsiveness of BRAF-mutant melanoma cell lines to the drug both in vitro and in mice.

They then analyzed S6 phosphorylation in tumor biopsies obtained from nine patients with BRAF-mutant melanomas before and after they had initiated treatment with a BRAF-targeted drug. Six patients had lower levels of tumor cell S6 phosphorylation after treatment compared with before treatment, and this was associated with an almost fivefold improvement in progression-free survival.

Finally, the researchers evaluated a method to rapidly monitor, in real time, levels of S6 phosphorylation in tumor cells. They found that they could reliably assess levels of S6 phosphorylation in tumor cells in fine-needle aspiration biopsies from patients before and during the first two weeks of treatment with a BRAF-targeted drug, and that in these patients , a decrease in S6 phosphorylation after treatment correlated with treatment response.

"Many of the signaling pathways known to drive various types of cancer regulate phosphorylation of S6, not just the BRAF pathway," said Corcoran. "Therefore, we are investigating whether S6 phosphorylation could be a biomarker of response to therapies that target these pathways in cancers other than melanoma."

More information: Abstract Number: C137

Presenter: Ryan B. Corcoran, M.D., Ph.D.

Title: Rapid assessment of TORC1 suppression as a functional biomarker predicting responsiveness to RAF and MEK inhibitors in BRAF-mutant melanoma patients

The clinical development of selective RAF and MEK inhibitors has transformed the treatment of the ~50% of melanoma patients whose tumors harbor BRAF mutations. However, a substantial percentage of these patients fail to respond to therapy, and most responses are partial and short-lived. Although multiple mechanisms of resistance have been identified in BRAF-mutant melanoma, no clinically useful biomarkers have been established to predict which patients are most likely to demonstrate sensitivity or resistance to RAF or MEK inhibitors. We found that suppression of TORC1 activity in response to RAF or MEK inhibitors, as measured by decreased phosphorylation of ribosomal protein-S6 (P-S6), was a functional biomarker that effectively predicted sensitivity in BRAF-mutant melanoma cell lines in vitro and in mouse tumor xenografts. In sensitive melanomas, TORC1 and P-S6 were suppressed in response to RAF or MEK inhibitors, but in resistant melanomas, TORC1 activity was maintained, in some cases despite robust suppression of MAPK signaling by these inhibitors. In mouse models, suppression of TORC1 after MAPK inhibition was necessary for induction of apoptosis and tumor response in vivo. Notably, in paired biopsies obtained from patients with BRAF-mutant melanoma before treatment and after initiation of RAF inhibitor therapy, P-S6 suppression was associated with significantly improved progression-free survival [HR 0.19, 95% CI 0.01-0.84, p=0.03]. Finally, we found that changes in P-S6 in patients' tumor cells could be readily monitored in real-time by multiplexed, quantitative immunofluorescence microscopy of serial fine-needle aspiration biopsies obtained from patients before and during the first 2 weeks of RAF inhibitor therapy. This approach provides a minimally-invasive means of rapidly monitoring the efficacy of

treatment, before changes in tumor volume are apparent by traditional radiographic imaging. Together, these results establish suppression of P-S6 after initiation of RAF inhibitor therapy as a robust potential functional biomarker to guide the treatment of patients with BRAF-mutant melanoma, and present a powerful methodology for monitoring changes in potentially any signaling pathway in response to targeted therapies in patients.

Provided by American Association for Cancer Research