Panel of melanoma mutations opens door to new treatment possibilities

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Researchers have developed a new genetic screening tool that will aid in the investigation of possible treatments for patients with melanoma and the unique genetic mutations that may accompany the disease, according to data presented at the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, held Nov. 12-16, 2011.

Heinz-Herbert Fiebig, M.D., Ph.D., associate professor of medical oncology at the University of Freiburg in Germany, presented data from 25 patient-derived melanoma models for which he and his colleagues studied relevant genetic mutations and the effect of new targeted and cytotoxic chemotherapeutic agents.

In this study, Fiebig, who is also the president and CEO of Oncotest GmbH Institute for Experimental Oncology, and colleagues collected melanoma samples from 80 patients. They were able to grow 38 of them in nude mice from which 25 permanent models were established. Eight different genetic mutations were determined in these models.

"The most prominent mutations were found in the BRAF oncogene; namely, 16 out of 25 tumors were positive for the mutation," said Fiebig.

About 25 percent of melanoma cases had a mutated NRAS gene. PI3Kalpha mutations were rare, and the screening found no mutations of the KRAS gene, which is a common genetic mutation in other forms of cancer.

The researchers then exposed the melanomas bearing specific mutations in vitro in the clonogenic assay to a variety of cancer treatments including traditional cytotoxic chemotherapy drugs, such as cisplatin, paclitaxel or vincristine, and modern chemotherapeutic drugs that target specific mutations, such as sorafenib and vemurafenib. They hoped to determine which, if any, of these drugs had an effect on the cancer cells and whether that effect was related to the presence or lack of a mutation.

The tests indicated that vemurafenib - or PLX-4720 - was most effective in melanoma tumor samples with the V600E mutation in the BRAF gene. This finding echoes those of recent clinical studies in humans. In addition, vincristine was found to only be effective in tumor samples that did not have a mutation in the BRAF gene. "Up until now, we were not able to detect other correlations between chemosensitivity against cytotoxic or targeted agents and other mutations," said Fiebig.

In the melanoma models, vemurafenib was 100 times more active in V600E-mutated melanomas compared with those melanomas with no mutations, Fiebig said. However, in the clinic, the majority of patients developed resistance within one year.

"Our melanoma models will allow researchers to investigate and overcome the possible underlying resistance mechanisms - for example, by combining vemurafenib with other target-specific agents," Fiebig said. "In addition, other new targeted drugs are being studied in a systematic way."

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