Scientist study skin cancer patients resistant to leading therapy

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Powerful drugs known as BRAF-inhibitors have been crucial for melanoma patients, saving lives through their ability to turn off the BRAF protein's power to spur cancer cell growth.

Yet they often work for only a year or less. Scientists know some of the DNA mutations that cause the drug resistance, but scientists have not been able to determine the underlying cause of the resistance in as many as a third of these patients. As a result, identifying genomic-based follow-up therapies for these patients has been a challenge.

Researchers at The University of Texas MD Anderson Cancer Center may have found a way to more accurately predict which patients will likely respond to genomic-based follow-up therapies, by looking at unique "protein patterns" in melanoma patients.

"There are patients whose DNA does not reveal how their melanomas became resistant to BRAF inhibitors," said Lawrence Kwong, Ph.D., instructor in Genomic Medicine at MD Anderson. "So we looked at patterns of changes in 150 proteins which can give clues to the causes of resistance, even when DNA sequencing data is uninformative."

Kwong is first author of a paper on the BRAF study, which appears in the Feb. 23 online edition of the *Journal of Clinical Investigation* (*JCI*).

"BRAF-inhibitors are effective in melanoma patients whose tumors have a 'hot spot' mutation in the BRAF cancer gene," said Lynda Chin, M.D., chair of Genomic Medicine, and corresponding author on the *JCI* paper. "Unfortunately, almost uniformly, these patients develop resistance to the drug. Therefore, figuring out how melanoma gets around the drug is a critical first step in identifying an alternative therapy for these patients once resistance develops, or better yet, a way to treat these patients with combinations that prevent the emergence of resistance."

Kwong and Chin's team analyzed BRAF inhibitor resistance, using a BRAF mouse melanoma model and human tumor biopsy samples. They found that such "proteome profiling" can provide a rapid view of BRAF-inhibitor resistance patterns in melanoma patients, at a fraction of the cost of DNA or RNA sequencing.

In addition to these findings, the study result also suggested the potential of using RNA and protein data as candidate "biomarkers" to help predict how long a patient will respond to BRAF inhibitor treatment so that combination or second-line therapies can be contemplated in a more personalized manner.

"These biomarkers include genes that track how fast the tumors are growing and how active the immune system is in the tumor," said Kwong. "This raises the possibility that pre-treatment biopsies can be used to guide decisions on targeted agents or immunotherapies that may be most effective for that individual patient."

However, the scientists caution that the study size was relatively small and will require additional analysis of much larger cohorts of patients.

Provided by University of Texas M. D. Anderson Cancer Center