MedicalXpress

Combo therapies tested to overcome drug resistance in melanoma patients

August 2 2011

About 50 to 60 percent of patients with melanoma have a mutation in the BRAF gene that drives the growth of their cancer. Most of these patients respond well to two novel agents being studied in clinical trials that inhibit the gene, with remarkable responses that are, unfortunately, almost always limited in duration.

In a study published today as a Priority Report in the peer-reviewed journal Cancer Research, scientists at UCLA's Jonsson Comprehensive Cancer Center tested a combination of small molecules that may, when used with the BRAF inhibitors, help overcome this drug resistance and extend the lives of those with advanced melanoma.

The team, led by researcher Dr. Roger Lo, focused on testing only small molecules that are already being studied in various phases of clinical trials in the hope of developing a combination treatment that can be studied in patients much more quickly than compounds that aren't yet being tested in humans.

"These molecules we tested are already being studied in patients with other cancers, and some of them have very good toxicity profiles with few side effects," said Lo, a Jonsson Cancer Center researcher and an assistant professor of dermatology and molecular and medical pharmacology. "The idea was to combine some of these with the BRAF inhibitors and come up with something that we don't have to wait years and years to use in patients. We need to find a way to combine these molecules so the cancer cell cannot get around them."

This study builds on the discoveries from a previous study published by Lo last year in the journal Nature. That study found that subsets of melanoma patients with BRAF mutations become resistant to BRAF inhibitors through either a genetic mutation in a gene called NRAS or the overexpression of a cell surface receptor protein.

It had been theorized that BRAF was finding a way around the experimental BRAF inhibitors by developing a secondary mutation in the same gene. However, Lo determined that was not the case, an important finding because it means that second-generation drugs targeting BRAF would not work and therefore should not be developed, saving precious time and money.

Lo and his team spent two years studying tissue taken from patients who become resistant to try to determine the mechanisms that helped the cancer evade the inhibitors. In the lab, they also developed drug resistant cell lines, in collaboration with another UCLA lab headed by Dr. Antoni Ribas, also a Jonsson Cancer Center researcher. There are still other mechanisms of resistance in melanoma patients with mutated BRAF who are treated with BRAF inhibitors, which UCLA researchers are seeking to uncover and that may provide even more targets for drug therapy.
Cancer operates similarly to a criminal seeking to evade his captors, and the small molecule inhibitors are like the police barricades that seek to block escape. When one of the cell signaling pathways driving resistance is blocked, the cancer finds a way to activate another pathway that will drive its growth. If that pathway is blocked, yet another pathway may be activated. The goal is to find a way to block all the pathways helping the cancer evade therapy at once so the cancer cells die before finding a way around the drugs.

In the lab, Lo and his team would apply one drug at a time to the resistant cancer cells and see what route or pathway the cancer used to

escape. They then determined what pathway was being used to evade therapy and found an inhibitor for that. In the end, the researchers identified the most optimal combination of molecules to block the pathways PI3K, mTORC and MEK.

"Normal cells have physiologic safety mechanisms to avert death and this is taken to a higher level by the cancer cell to serve its growth agenda, making single agent targeted therapy insufficient," Lo said. "We have to block several roads, which is what is behind our approach to developing combination therapies. The key was to figure out how to combine the molecules so that the cancer cannot get around them. Why wait for the cancer to escape? Let's block all the pathways right from the start."

Lo said this study highlights the need not only to identify mechanisms of acquired resistance to targeted inhibitors, but also to understand the signaling network associated with each mechanism to generalize potential translatable approaches to overcome drug resistance.

Once the right combinations of drugs were used together, the inhibitors "consistently triggered cell death in a highly efficient and consistent manner," the study states. "Together, our findings offer a rational strategy to guide clinical testing in pre-identified subsets of patients who relapse during treatment with BRAF inhibitors."

Lo said a clinical trial could be planned that first examines the patients' cancers to identify the resistance mechanisms at play. Those patients could then be funneled into a study pairing the inhibitors that target those specific pathways. Patients with other resistance mechanisms at work would be placed in studies testing inhibitors specific to their resistance mechanisms.

The next step, Lo said, is to identify all the mechanisms of resistance in

this form of melanoma.

Provided by University of California - Los Angeles Health Sciences