Genomic deletions explain why some types of melanoma resist targeted therapies

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Melanoma is the deadliest form of skin cancer. With global incidence rates rising, new, more effective treatments are necessary to alleviate the health burden of the disease. Important advances in recent years include doctors using genetic tests to look for specific mutations they can target for more personalized, effective treatment.
Around one in two melanoma patients will have mutations in the BRAF gene. This gene normally makes a protein that helps control cell growth, but mutations can cause the cells to grow and divide uncontrollably instead, happening in many different types of cancer including melanoma.

The discovery of BRAF mutations has led to development of targeted therapies to inhibit its function. One of the standard treatment options for melanoma over the last 10 years has been to simultaneously target both BRAF mutations and MEK. These two genes are part of the MAPK signaling pathway, which, in cancer, is rewired for uncontrolled growth. Targeting two different critical points in the same domino chain helps slow or stop cancer growth.

Despite great initial responses to the combined use of the first-generation inhibitors, around 50% of melanoma patients with BRAF mutations will relapse within one year. The cancer acquires resistance to the drugs, finding other ways to reactive the MAPK pathway through mechanisms that remain poorly understood.

"Melanoma drug resistance is a huge clinical problem because it occurs in almost all BRAF-mutated patients under BRAF/MEK inhibitor therapy and there are few or no therapeutic alternatives. There is an urgent need to understand the many different underlying mechanisms and find new strategies to deal with this constantly evolving arms race," says Dr. Francisco Aya Moreno, a medically-trained oncologist and recent Ph.D. graduate at the Center for Genomic Regulation (CRG) in Barcelona.

A study published in the journal Cell Reports has disentangled the mechanisms behind one of the ways cancer cells develop resistance to targeted therapy.
The study found that, in response to treatment, melanomas can 'break' parts of their BRAF gene, also known as genomic deletions. This helps the tumor create alternative versions of the protein (altBRAFs) which lack regions targeted by BRAF inhibitors, reactivating the MAPK pathway and making the drugs less effective. The finding was consistent across various lab models and patient tumor samples.

The findings are important because altBRAFs were thought to be made through alternative splicing, which is when cells use the same gene to synthesize different proteins. The discovery that genomic deletions, and not splicing, are the cause means a shift away from previous proposals for using drugs that target splicing as a therapeutic strategy.

"For years, we've known that some patients produce altBRAFs and these help the cancer resist treatment, but we misunderstood the mechanism behind their creation. Knowing that genomic deletions are the cause opens new avenues for developing therapies that could more effectively help patients with BRAF mutations," explains ICREA Research Professor Juan Valcarcel, co-author of the study and researcher at the Center for Genomic Regulation.

Surprisingly, the researchers found evidence of the same genomic deletions in melanomas that hadn't been treated yet. In other words, melanomas can naturally develop mechanisms that mimic drug resistance, even without exposure to drugs. Identifying and targeting these early resistance mechanisms through profound genetic testing in a clinical setting before treatment begins could improve the efficacy of first-line therapies.

Even more surprisingly, further analyses revealed that genomic deletions might be a more widespread mechanism of oncogenesis and resistance than previously thought. Though uncommon, researchers found evidence of altBRAFs in melanomas with a normal-functioning BRAF gene, as
well as in other types of cancer including non-small cell lung cancer, breast cancer, kidney cancer and prostate cancer. The findings could increase the patient population benefiting from targeted treatments which are currently under clinical development.

"There is an emerging class of drugs known as second generation RAF inhibitors. Unlike BRAF inhibitors, these drugs have a broad spectrum, and so could potentially inhibit the function of altBRAFs. Clinical trials which are assessing their effectiveness should also expand to include melanoma patients with a normal functioning BRAF gene as well, and possibly to other cancer types which express altBRAFs," explains Dr. Aya Moreno.

Dr. Aya Moreno is part of the second cohort of the Ph.D.4MD program, a joint effort by Center for Genomic Regulation (CRG), the Institute for Research in Biomedicine (IRB Barcelona), the August Pi i Sunyer Biomedical Research Institute (IDIBAPS) and the Vall d'Hebron Research Institute (VHIR) designed to leverage the medical insight of a doctor to drive research that benefits patients.

"Having the opportunity to approach this research with both a clinician's perspective and a scientist's curiosity has been invaluable. It allowed us to uncover not just how melanomas resist treatment but also how this knowledge could lead to more effective therapies for patients. This fusion of clinical insight and scientific investigation is crucial for making real progress in our fight against cancer," concludes Dr. Aya Moreno.

The study was led by Dr. Aya Moreno and co-supervised by Professor Juan Valcarcel at the Center for Genomic Regulation and Dr. Ana Arance at IDIBAPS.

It was also carried out in collaboration with Nuria López Bigas' research
group at IRB Barcelona.

More information: Genomic deletions explain the generation of alternative BRAF isoforms conferring resistance to MAPK inhibitors in melanoma, Cell Reports (2024). DOI: 10.1016/j.celrep.2024.114048. www.cell.com/cell-reports/full ... 2211-1247(24)00376-0

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