Drug combination against NRAS-mutant melanoma discovered
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A new study published online in *Nature Medicine*, led by scientists at The University of Texas MD Anderson Cancer Center, describes the discovery of a novel drug combination aimed at a subset of melanoma patients who currently have no effective therapeutic options.

Melanoma patients have different responses to therapy, depending on what genes are mutated in their tumors. About half of melanomas have a mutation in the BRAF gene; while a quarter have a mutation in the NRAS gene.

New BRAF inhibitor drugs are effective against BRAF-mutant melanoma, but no comparable therapies are currently available against NRAS-mutant melanoma. For the first time, this study provides new hope for patients with NRAS-mutant melanoma that an effective targeted treatment might be developed in the coming years.

By analyzing a sophisticated, genetically engineered mouse model of NRAS-mutant melanoma with a novel systems biology approach, scientists discovered that combining two different classes of drugs shrinks these tumors.

The researchers, led by Lynda Chin, M.D., chair of the Department of Genomic Medicine and scientific director of the Institute for Applied Cancer Science, at MD Anderson – together with colleagues from the Dana-Farber Cancer Institute at Harvard Medical School and from Boston University – discovered that the two drugs, which inhibit proteins Mek and Cdk4, complement one another by targeting unique cancer features.

"The lack of a drug like the BRAF inhibitor that works against NRAS means that there is still no effective treatment option for NRAS-mutant patients to fall back on," said Chin. "Developing an effective combination using existing drugs or drugs already in clinical development is a path to address this unmet need for this population of melanoma patients."

A roadmap for effective drug combinations

Researchers must first know what an effective treatment actually looks like before they can identify and develop effective drug combinations. To accomplish this, Chin and her colleagues generated an inducible NRAS (iNRAS) mouse model. In the model, activating mutant NRAS caused melanomas to form, while turning it off caused the melanomas to shrink – exactly what an effective drug therapy should do.

"We had this great mouse model where the tumors disappear using a genetic trick, and we realized that it was essentially a model of 'the perfect targeted therapy'. So we decided to use it as 'road map' to guide us toward effective drug combinations," said lead author Lawrence Kwong, Ph.D., an instructor in MD Anderson’s Department of Genomic Medicine.

The researchers speculated that comparing the molecular effects of a drug versus genetically switching off mutant NRAS would reveal what mechanism(s) the drug lacks to be effective. With this knowledge, a complementary secondary drug could be identified which, in combination with the first, would achieve a similar effect to shutting off mutant NRAS.

The researchers used Mek inhibitors as a starting point because these drugs are already in late stage clinical development in which they have been shown to slow tumor growth without shrinking them. The goal of this study was to identify additional inhibitors to combine with the Mek inhibitors to shrink NRAS mutant melanomas.

Using genomic technologies, including transcriptomic profiling, combined with a mathematical systems biology approach called Transcriptional Regulatory Associations in
Pathways (TRAP), Kwong and colleagues identified Cdk4 as a target that is predicted to provide a synergistic effect when co-inhibited along with Mek. TRAP is a network model that evaluates complex biological interactions mathematically.

Cdk4, Cyclin-dependent kinase 4, is a major regulator of cell proliferation, the process of cells dividing to produce more cells. Cancer cells often hijack Cdk4 as a way to grow rapidly.

When researchers combined the Cdk4 and Mek inhibitors in four different model systems, the drug combination produced a synergistic effect and shrunk tumors, validating the mathematical and experimental predictions.

"This is exciting because our study used a novel approach," said Kwong. "We combined a preclinical model – the iNRAS mouse – with powerful genomic and computational science to identify an effective combination of already-available drugs. This is a great proof-of-concept that preclinical studies in the mouse can inform the clinical development of drugs for patients."

**A dimmer switch dialing down tumors**

The molecular answer behind the synergistic effect can be explained like a dimmer switch on a household light bulb, where NRAS is not a simple on-off switch that either causes tumors to grow or to shrink. Using the Mek inhibitor by itself was like turning the dimmer switch only halfway down – it was able to coax many tumor cells to die, but the remaining cells kept growing. The addition of the Cdk4 inhibitor, which by itself would have little effect, directly inhibited the cell cycle machinery to halt cell growth. The net effect of driving cancer cells to die without the ability to grow is tumor shrinkage.

"This new way of thinking about RAS signaling opens new opportunities to target other important signaling pathways in cancer, and the approach we have taken can now inform similar efforts to develop non-obvious combination strategies for other RAS mutated cancers," said Chin.