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A two-for-one approach to boost melanoma immunotherapy

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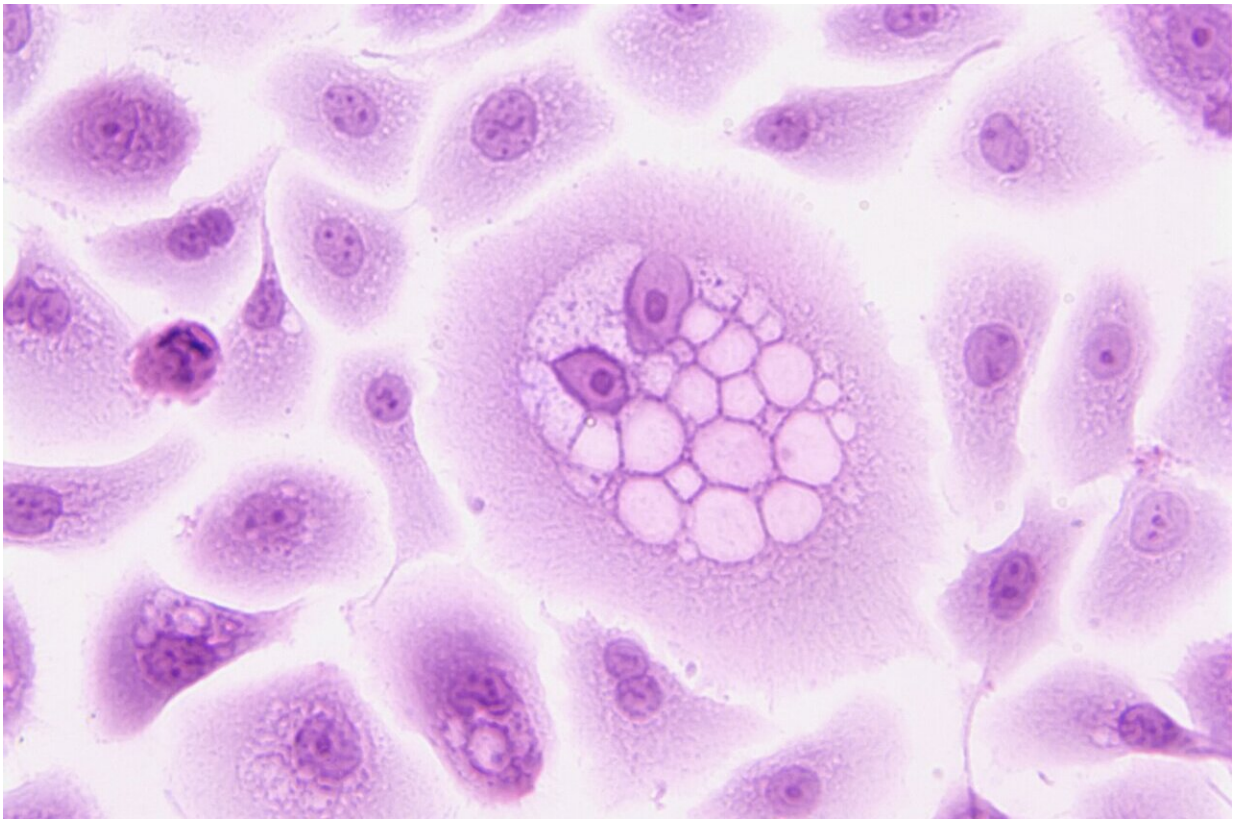

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New research from Sanford Burnham Prebys has helped explain how melanoma evades the immune system and may guide the discovery of future therapies for the disease. The study found that a protein known to

be active in immune cells is also active inside melanoma cells, helping promote tumor growth. The findings, published in the journal *Science Advances*, suggest that targeting this protein with new drugs may deliver a powerful double hit to melanoma tumors.

"The immune system's control of a tumor is influenced by both internal factors within tumor cells, as well as factors from the tumor's surroundings," says first author Hyungsoo Kim, Ph.D., a research assistant professor at Sanford Burnham Prebys in the lab of senior author Ze'ev Ronai, Ph.D. "We found that the protein we're studying is involved in both, which makes it an ideal target for new cancer therapies."

One of the most significant breakthroughs in cancer therapy in the last century is the development of immunotherapy, an approach that helps improve the immune system's ability to fight cancer on its own without the use of toxic chemotherapy drugs.

"Immunotherapy is the first-line therapy for several cancers now, but the success of immunotherapy is limited because many cancers either don't respond to it or become resistant over time," says Kim. "An important goal remains to improve the effectiveness of immunotherapy."

To find ways to boost immunotherapy in melanoma, the research team analyzed data from patient tumors to identify genes that may coincide with patients' responsiveness to immunotherapy. This led to the identification of a protein that helps tumors evade the immune system—called NR2F6—which was found not only in tumor cells, but also in the surrounding noncancerous cells.

"Often we find that a protein has the opposite effect outside of tumors compared to what it does within a tumor, which is less effective for therapy," says Kim. "In the case of NR2F6, we found that it elicits the same change in the tumor and in its surrounding tissues, pointing to a

synergistic effect. This means that treatments that block this protein's activity could be twice as effective."

To confirm their findings in mice, the researchers genetically removed the NR2F6 protein in both melanoma tumors and in the tumors' environment. This inhibited melanoma growth more strongly, compared to when this effect occurs in either the tumor or its microenvironment alone. The cancer's response to immunotherapy was also enhanced upon loss of NR2F6 in both tumors and their microenvironment.

"This tells us that NR2F6 helps melanoma evade the immune system, and without it, the immune system can more readily suppress tumor growth," adds Kim.

To help advance their discovery further, the team is working with the Institute's Conrad Prebys Center for Chemical Genomics to identify new drugs that can target NR2F6.

"Discovering drugs that can target this protein are expected to offer a new way to treat melanomas, and possibly other tumors, that would otherwise resist immunotherapy," says Kim.

More information: Hyungsoo Kim et al, Melanoma-intrinsic NR2F6 activity regulates anti-tumor immunity, *Science Advances* (2023). DOI: 10.1126/sciadv.adf6621. www.science.org/doi/10.1126/sciadv.adf6621

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