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Researchers ID new target in drive to improve immunotherapy for cancer

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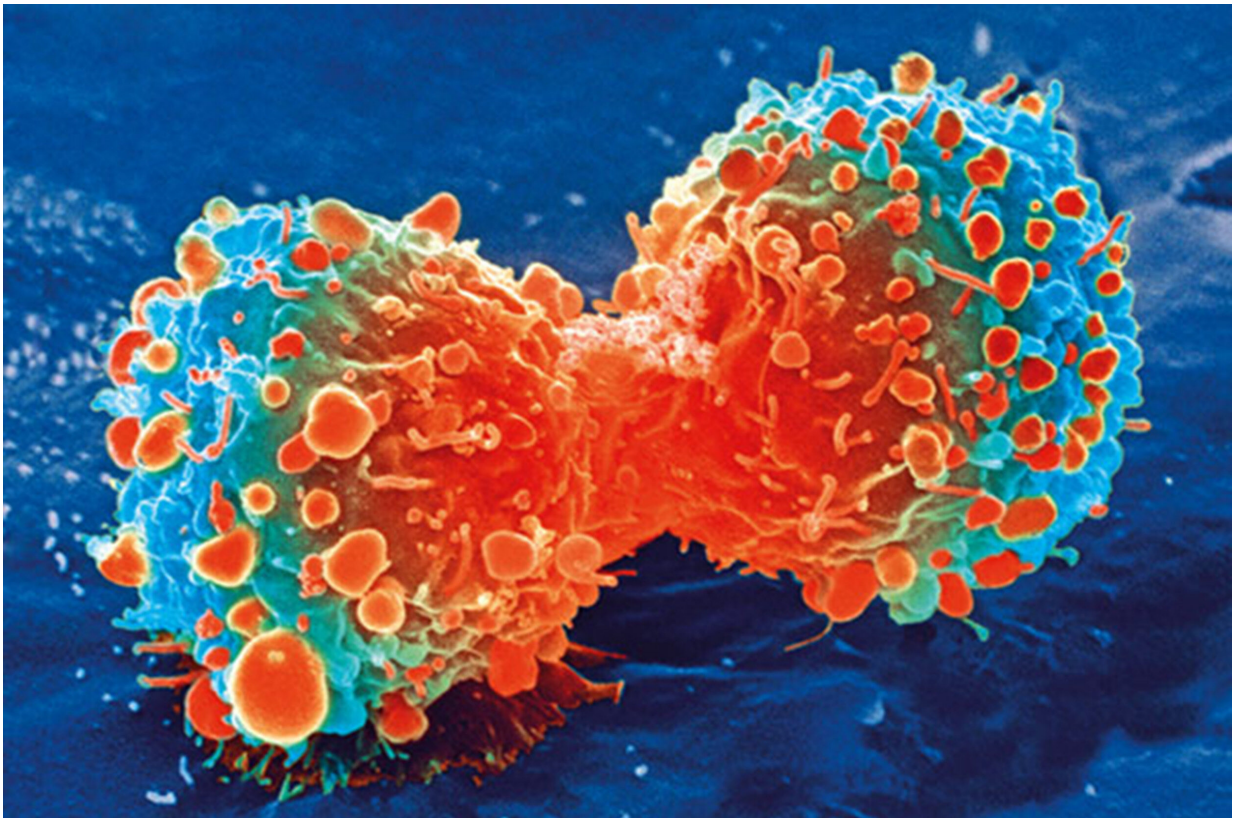

Cancer cell during cell division. Credit: National Institutes of Health

Researchers at the UCLA Jonsson Comprehensive Cancer Center and UCLA School of Dentistry have identified a potential new combination therapy to treat advanced head and neck squamous cell carcinoma, the

most common type of head and neck cancer.

A study in mice found that using an anti-PD1 immunotherapy drug in combination with PTC209, an inhibitor that targets the protein BMI1, successfully stopped the growth and spread of the cancer, prevented reoccurrences and eliminated cancer stem cells. This is the first preclinical study to provide evidence that targeting BMI1 proteins enhances immunotherapy and eliminates cancer stem cells by activating antitumor immunity.

Immunotherapies using PD1 blockade have transformed the way people with difficult cancers are treated. Currently, PD1 blockade combined with chemotherapy is approved for recurrent or metastatic head and neck cancer, giving people whose disease would have otherwise been seen as a death sentence another option. However, response rates are not very high and response duration is relatively short, indicating that this type of cancer might be resistant to PD1 blockade.

To help overcome immunotherapy resistance, UCLA researchers have been studying the role of cancer stem cells and the protein BMI1. Growing evidence suggests cancer stem cells might be responsible for such resistance, as well as for relapse or reoccurrence, and BMI1, which functions in several cancers, including head and neck, has been found to control cancer stem cells' self-renewal. Targeting cancer stem cells may be critical for improving the efficacy of immunotherapy and preventing tumor relapse.

The team used a mouse model of head and neck squamous cell carcinoma that fully mimicked human cancer development and metastasis, allowing them to perform lineage tracing of BMI1-positive cancer stem cells in an undisturbed tumor immune microenvironment. They then tested whether BMI1 cancer stem cells could be eradicated by PD1 blockade-based combination therapy using both pharmacological

and genetic inhibition of BMI1. They found that inhibiting BMI1 not only helped eliminate the BMI1 cancer stem cells but also enhanced PD1 blockade by activating tumor cell-intrinsic immunity, which inhibited metastatic tumor growth and prevented tumor relapse.

Many people with advanced head and neck cancers who are treated with PD1 blockade and chemotherapy eventually see their cancer return and become resistant to the therapy. This preclinical study provides an important foundation for developing a new PD1 blockade-based combination therapy with BMI1 inhibitors that have the potential to help overcome resistance to the immunotherapy.

More information: Lingfei Jia et al, BMI1 inhibition eliminates residual cancer stem cells after PD1 blockade and activates antitumor immunity to prevent metastasis and relapse, *Cell Stem Cell* (2020). DOI: 10.1016/j.stem.2020.06.022

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