Preclinical study uncovers two proteins' crucial role in causing cancer cell growth

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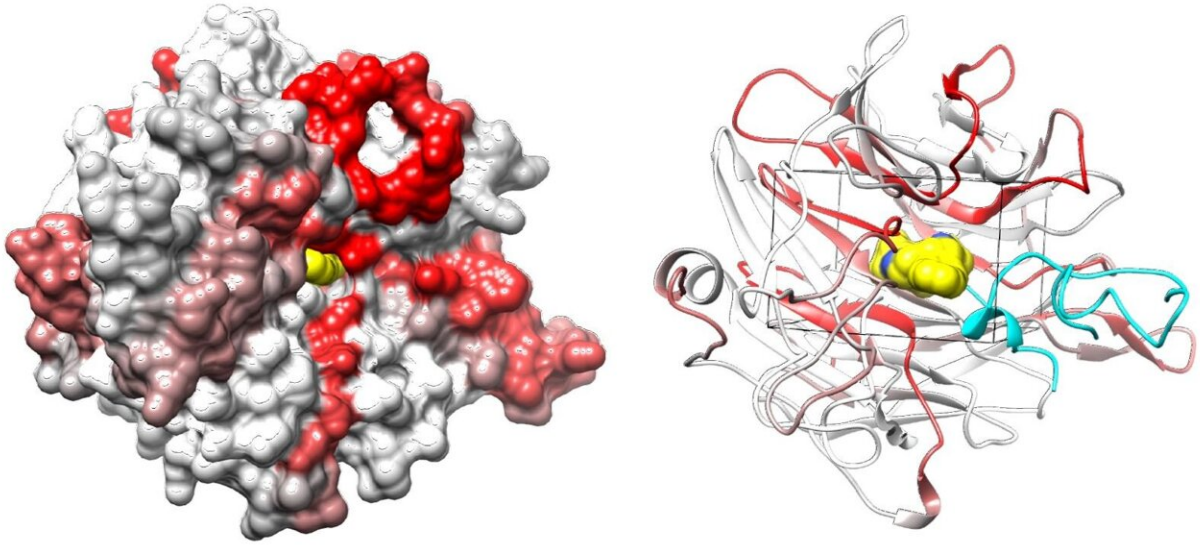

Protein surface (left) and ribbon (right) models of integrin αV's β-propeller domain illustrate the capacity of Cpd_AV2 (yellow) in disrupting the interaction between integrin β5's βA loop (cyan; green indicates the key interacting residue lysine 287) and integrin αV. The integrin αV's β-propeller domain is colored by normalized CRISPR-tiling score (NCS). Credit: Chun-Wei (David) Chen, Ph.D. / City of Hope

Scientists at City of Hope, one of the largest cancer research and treatment organizations in the United States, have discovered a new cellular mechanism that plays an important role in cancer cells' ability to cause disease. The study is published in *Nature Structural & Molecular*

Biology.

A team led by Chun-Wei (David) Chen, Ph.D., an associate professor of systems biology at City of Hope, pinpointed two cell-surface proteins, integrin αV and β5, that partner to spur cancer cell growth. The researchers next identified a region of integrin αV called the β-propeller domain that controls interaction between the two proteins.

Blending laboratory experiments with computer simulations, Chen's team created a powerful digital application of CRISPR gene-tiling technology to uncover potential cancer medicines that precisely target the β-propeller domain.

After identifying the chemical compound Cpd_AV2 as a strong candidate, the team applied this compound to human cancer cells in the laboratory. Integrin αV and β5 rapidly separated, dissolving communication between the two proteins and causing cellular death, effectively halting growth in cancer cell lines.

Clinically, the researchers found integrin αV overexpression in multiple cancer types, highlighting integrin αV's lead role in cancer progression. High levels of integrin αV were also associated with a poor prognosis in 3,700 patients with cancers of the breast, pancreas, liver, lung and brain.

By expanding opportunities for developing targeted therapies that sever the connection between integrin αV and β5, the City of Hope-led findings suggest a potent new approach for cancer treatment and future medicine discovery studies.

"Our study showcases an innovative application of CRISPR gene-tiling technology, revealing previously undiscovered sites on proteins with the capacity to cause cancer," said Chen, who is also division director of epigenetic and transcriptional engineering at Beckman Research Institute

of City of Hope.

"This breakthrough opens new avenues for the advancement of next-generation oncologic therapies, marking a significant milestone in City of Hope's battle against cancer."

Scientists estimate that up to 1,100 different proteins live on the plasma membrane, or semi-permeable surface of the cancer cell; many of these proteins' biological functions could influence disease progression and therapeutic response. The region offers a valuable pool of targets for medical intervention because there are plenty of surface receptors and signaling proteins that can be engineered to aid in the delivery of cancer treatments.

Integrin αV and β5 belong to the integrin family, a group of cell-surface receptors that play a central role in regulating cellular interactions, particularly across cell membranes.

More information: A novel class of inhibitors that disrupts the stability of integrin heterodimers identified by CRISPR-tiling-instructed genetic screens, *Nature Structural & Molecular Biology* (2024). DOI: 10.1038/s41594-024-01211-y

Provided by City of Hope National Medical Center

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