New Approach Attacks 'Undruggable' Cancers From the Outside In

This method targets one of the most common drivers of lung, colorectal, and pancreatic cancer.

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Cancer researchers have made great strides in developing targeted therapies that treat the specific genetic mutations underlying a patient's cancer. However, many of the most common cancer-causing genes are so central to cellular function throughout the body that they are essentially "undruggable." Now, researchers at UC San Francisco have found a way to attack one of the most common drivers of lung, colorectal, and pancreatic cancer by targeting the proteins it produces on the outside of the cell.

Their study, published January 23 in the journal eLife, reveals that cancer-causing mutations in RAS, a family of genes found in all animal cell types, creates tell-tale changes in a community of proteins on the surface of cancer cells. The researchers show that attacking these cells from the outside in—by targeting the altered proteins with antibodies—could be a viable therapeutic approach for previously undruggable cancer targets.

RAS serves as a major communication hub that relays information from outside the cell to as many as 12 different signaling pathways inside the cell, including the MAPK and PI3K pathways, which then collectively induce changes to our cells. Nearly one third of all human malignancies are caused by one of the three RAS isoforms (KRAS, NRAS and HRAS) being activated by a mutation, making RAS an important focus in cancer research.

"While there are intense efforts to target signaling pathways within the cell, very little is understood about how RAS signaling can regulate the set of proteins expressed on the surface of a cell at any time," said senior author James Wells, PhD, professor of pharmaceutical chemistry and member of the Helen Diller Family Comprehensive Cancer Center at UCSF. "More studies in this area would help us understand how mutations in RAS signaling drive malignancy, and may point to novel targets for antibody and cellular-therapy-based treatment in RAS-driven cancers."

Wells, who holds the Harry Wm. and Diana V. Hind Distinguished Professorship in Pharmaceutical Sciences at UCSF, began looking into the influence of RAS signaling on the proteins present on the surface of cells. Using an analytical technique called mass spectrometry, his team studied a particular cell line called MCF10A and discovered a signature of surface proteins that change when cells are transformed with a KRAS mutation called KRAS G12V, and driven by MAPK pathway

signaling.

Next, the team generated a toolkit of antibodies that target seven of these RAS-induced proteins. Applying the antibodies to their targets revealed that five of the proteins are broadly distributed on cell lines harboring KRAS mutations. A parallel study using a cell-surface CRISPRi screen—which uses CRISPR-Cas9 technology to temporarily switch off specific genes in order to investigate their function—later found that signaling proteins involved in integrin and Wnt signaling are critical to RAS-transformed cells.

Most strikingly, the researchers observed that one protein, CDCP1, was a common target in both studies. CDCP1 has previously been identified as a driver of cancer-cell growth, metastasis and tumor progression. The team then showed that antibodies against CDCP1 could be used to deliver cytotoxic or immunotherapeutic compounds to Ras-mutant cancer cells in the lab, and as a reporter of RAS signaling in a mouse xenograft model of pancreatic cancer.

“While our results provide a large number of interesting proteins to follow up, we decided to focus on targeting CDCP1,” said study first author Alexander Martinko, an NSF graduate research fellow at UCSF. “Our antibodies did not appear to inhibit CDCP1, but we were motivated by the fact that it was over-expressed in many RAS-driven cell lines. This suggests that it could be an attractive target for an antibody-drug-conjugate treatment.”

“Overall, we’ve presented a novel technological pipeline for the discovery and application of antibodies to surface proteins regulated by cancer-causing signaling pathways,” Wells said. “Ultimately, we hope this pipeline can be used to attack undruggable targets, including RAS, from the outside.”

Additional authors on the study included Charles Truillet, PhD, Olivier Julien, PhD, Juan Diaz, PhD, Max A Horlbeck, Jonathan S Weissman, PhD, Sourav Bandyopadhyay, PhD, and Michael Evans, PhD, of UCSF; and Gordon Whiteley, PhD, and Josip Blonder, MD, of the Frederick National Laboratory for Cancer Research.

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