

CANCER DISCOVERY

Nanostars Amplify Ability to Image Cancer

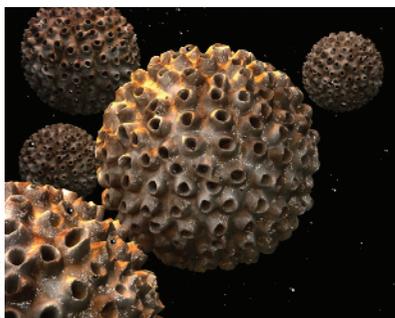
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Researchers have uncovered genomic abnormalities that drive some head and neck cancers. For example, some tumors that tested positive for human papillomavirus (illustrated above) had recurrent deletions and truncating mutations in *TRAF3*.

The researchers uncovered genomic abnormalities that help explain the origin and progression of the cancers. For instance, they discovered that some HPV-positive tumors had recurrent deletions and truncating mutations in *TRAF3*. This gene is crucial for defense against several viruses, and its absence might impair the immune system's ability to clear HPV.

The study also suggests new treatment avenues and ways to pinpoint patients likely to benefit from therapy. Among HPV-negative patients, Hayes and colleagues found a subset that showed a three-gene signature: normal *TP53*, mutations that inactivate the cell-death gene *CASP8*, and mutations that activate *HRAS*, which promotes cell division. Clinical records indicate that these patients have more favorable outcomes, and the signature could enable doctors to identify those who could be treated successfully with less-aggressive therapy.

In addition, one third of head and neck cancers have amplifications of the cell cycle regulator *CCND1*, the team discovered. CDK4/6 inhibitors, such as the recently approved drug palbociclib (Ibrance; Pfizer), disrupt this pathway. The paper supports testing these inhibitors in head and neck cancer, Hayes says.

"This study is important because it's laying the foundation for the genomic and molecular characterization of the disease," says Thomas Ow, MD, of the Montefiore Einstein Center for Cancer Care in New York, NY, who wasn't connected to the research.

Information on all 528 patients, not just the initial group of 279, is now available through www.cancergenome.nih.gov. ■

A Potential Epigenetic Therapy for NSCLC

Beyond targeted treatments for non-small cell lung cancer (NSCLC), researchers are increasingly exploring the potential of therapies that influence DNA methylation and histone modification—two epigenetic processes frequently disrupted in cancer—against this disease.

One such epigenetic target is EZH2, a protein that silences various genes by adding methyl groups to histone H3, causing chromatin compaction. "High EZH2 expression correlates with a poor prognosis for NSCLC, which is why we decided to investigate the therapeutic possibilities of drugs that inhibit this enzyme," says Carla Kim, PhD, an associate professor at Boston Children's Hospital in Boston, MA. She recently showed that EZH2 suppression may boost the sensitivity of two NSCLC subsets to etoposide, a standard chemotherapy that works in only a minority of patients (Nature 28 Jan 2015 [Epub ahead of print]).

When Kim and her team blocked EZH2 in NSCLC cells, they observed two distinct phenotypes: Some cells became more sensitive to etoposide, while others became more resistant to the drug's effects. The researchers found that the majority of sensitized cells harbored inactivating mutations in *BRG1* or activating mutations in *EGFR*. On the other hand, cells resistant to etoposide in the wake of EZH2 inhibition were nearly all wild-type for both genes. In an *EGFR*-mutant mouse model of NSCLC, combining etoposide with EZH2 suppression significantly impeded tumor growth; however, this dual therapy was ineffective in mice with wild-type *EGFR* and *BRG1*.

Unlike EZH2, BRG1 remodels chromatin into a more open structure and helps topoisomerase II (TopoII)—the target of etoposide—ensure that DNA daughter strands separate completely during replication. "Without BRG1, TopoII can't do its job," says Christine Fillmore, PhD, a postdoctoral fellow in the Kim laboratory and the study's first author.

The researchers noted that in *BRG1*-mutant NSCLC cells—rendered still

more vulnerable to etoposide by EZH2 inhibition—the number of anaphase bridges, or entangled DNA daughter strands, increased, as did the rate of programmed cell death. *EGFR*-mutant NSCLC cells, also acutely sensitive to combined EZH2 suppression and etoposide, behaved similarly despite having wild-type *BRG1*. "For reasons we don't yet understand, *EGFR*-mutant cells aren't able to fully utilize BRG1, even though it's present," Fillmore says.

"The clinical implications of our research are exciting," Kim says, "because there are no specific drugs for *BRG1*-mutant NSCLC, and the *EGFR*-mutant subset inevitably becomes resistant to targeted therapy."

"This study opens the door to a closer investigation of dual EZH2 and TopoII inhibition in certain disease settings," agrees Katerina Politi, PhD, an assistant professor at Yale Cancer Center in New Haven, CT, who wasn't involved in the research. "It's a great example of how understanding the molecular consequences of specific mutations can inform the use of standard chemotherapy."

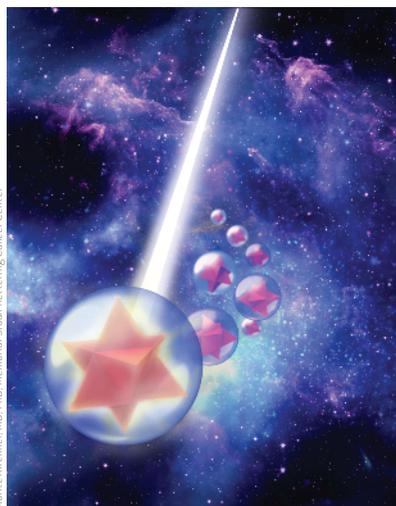
Kim and Fillmore hope their findings will also guide patient selection for EZH2 inhibitors in development—there are several in clinical trials, although none is yet approved. "We still have to consider the tumor genotype, even with epigenetic therapy," Kim says. ■

Nanostars Amplify Ability to Image Cancer

Most cancer imaging techniques rely on probes linked to tumor-specific targets. New research has shown that one nanoparticle without ligands can detect five different cancers in mice. These "nanostars" boost surface-enhanced resonance Raman scattering signals enough to visualize tumor margins, microscopic metastases, and even precancerous cells.

"With this ultra-bright probe, we can now really see cancer, no matter how small, no matter what type," says Moritz F. Kircher, MD, PhD, a radiologist at Memorial Sloan Kettering Cancer Center in New York, NY, and senior investigator in the study (Sci Transl Med 2015;7:271ra7).

NEWS IN BRIEF



Moritz Kircher, MD, PhD, Memorial Sloan-Kettering Cancer Center

A schematic representation of surface-enhanced resonance Raman scattering nanostars. Given their unique shape and resonance, the nanostars were 400 times more sensitive in detecting cancer than their non-resonant, spherical counterparts.

In Raman imaging, a laser beam hits the nanostars and generates a unique scatter pattern. “Reporter” molecules embedded within the nanoparticle shift how the incoming photons scatter, creating a spectral “fingerprint” that wouldn’t normally be found in the body. Then a camera records the spectra and transforms them into spots of light. Unlike normal cells, tumor cells preferentially draw in nanostars through an enhanced uptake process called macropinocytosis, says Kircher. Therefore, no specific targets are needed for Raman imaging to expose cancer hiding in tissue that looks healthy.

In previous work, Kircher and his colleagues used sphere-shaped nanoparticles with Raman imaging to precisely outline glioblastomas in mice. However, for reasons that aren’t yet fully understood, other tumor types don’t always accumulate enough nanospheres to generate sufficient light.

To improve the chances of “seeing” cancers that contain low probe concentrations, Kircher redesigned the nanoparticle and increased Raman signals 400-fold. Innovations included changing the gold core into a star shape, which helped concentrate the

signal at each pointed tip. The new geometry also shifts absorbed light to the near-infrared region, further strengthening the signal by making it resonate at wavelengths that are shared by the laser, the gold core, and the red dye Raman reporter that coats the gold core.

Four transgenic mouse models of cancer and one human sarcoma xenograft model were used to evaluate the nanostar probe. Researchers chose models that mimic tumor growth in human cancers known to have high incidence, morbidity, mortality, or recurrence: breast cancer, pancreatic ductal adenocarcinoma, prostate cancer, and sarcoma. Each test group, which included four to seven mice, received 30 fmol/g intravenous injections of nanostars.

After waiting 16 to 18 hours for the nanostars to clear general circulation and become internalized by tumor cells, surgeons excised the tumors identified by routine light imaging. Researchers then examined the remaining normal-appearing mouse tissue with Raman imaging and compared the results from that analysis with histopathologic findings. In every instance, Raman imaging revealed neoplastic cells that careful surgical resection had left behind. Furthermore, two of the mouse models—for pancreatic and prostate neoplasia—also revealed nanostars in surrounding epithelial cells. These intraepithelial foci were histologically confirmed as pre-malignant stages known to progress to invasive cancers.

“This is a big step forward,” says Adam de la Zerda, PhD, an assistant professor of structural biology at Stanford University School of Medicine in Palo Alto, CA, who was not involved in this study. Fluorescence imaging methods rely on biological molecules, whereas “the benefit of Raman is that our bodies produce absolutely no similar signal,” de la Zerda says. “We want to be able to detect these rogue cancer cells when they invade neighboring tissue. This technique has the potential to do that.” ■

NOTED

- **The biopharmaceutical company AbbVie announced it will acquire Sunnyvale, CA-based Pharmacyclics** in a deal valued at approximately \$21 billion. Pharmacyclics’ lead drug is ibrutinib (Imbruvica), a Bruton’s tyrosine kinase inhibitor approved to treat three types of blood cancer: chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenström macroglobulinemia.
- After serving as the agency’s commissioner for nearly 6 years, **Margaret Hamburg, MD, left the FDA at the end of March**. Stephen Ostroff, MD, the FDA’s chief scientist, is serving as acting commissioner.
- **The FDA approved the use of nivolumab (Opdivo; Bristol-Myers Squibb [BMS]) to treat patients with metastatic squamous non-small cell lung cancer** whose disease progressed on or after platinum-based chemotherapy. A PD-1 inhibitor, nivolumab was approved in December to treat advanced melanoma.
- **BMS announced three deals that will expand its oncology pipeline.** The company will acquire San Carlos, CA-based Flexus Biosciences, a biotech developing IDO and TDO inhibitors, in a deal worth up to \$1.25 billion. BMS also signed an agreement worth up to \$975 million with Bavarian Nordic of Kvistgaard, Denmark, to license and commercialize Prostavac, a phase III immunotherapeutic “vaccine” for the treatment of metastatic castration-resistant prostate cancer. Finally, BMS will work with Rigel Pharmaceuticals of South San Francisco, CA, to develop small-molecule TGFβ receptor kinase inhibitors, potentially netting Rigel more than \$339 million.
- **NIH Director Francis Collins, MD, PhD, testified in support of his agency’s budget request of \$31.31 billion for fiscal year (FY) 2016**, a 3.3% increase over FY2015, before the House Appropriations Subcommittee on Labor, HHS, Education, and Related Agencies. He said that the request would fund 1,227 more research grants than in FY2015 and that it “allocates resources to areas of the most extraordinary promise for biomedical research while maintaining the flexibility to pursue unplanned scientific opportunities and address unforeseen health needs.”

For more news on cancer research, visit *Cancer Discovery* online at <http://CDnews.aacrjournals.org>.