Gene mutations that contribute to head and neck cancer also provide 'precision' treatment targets

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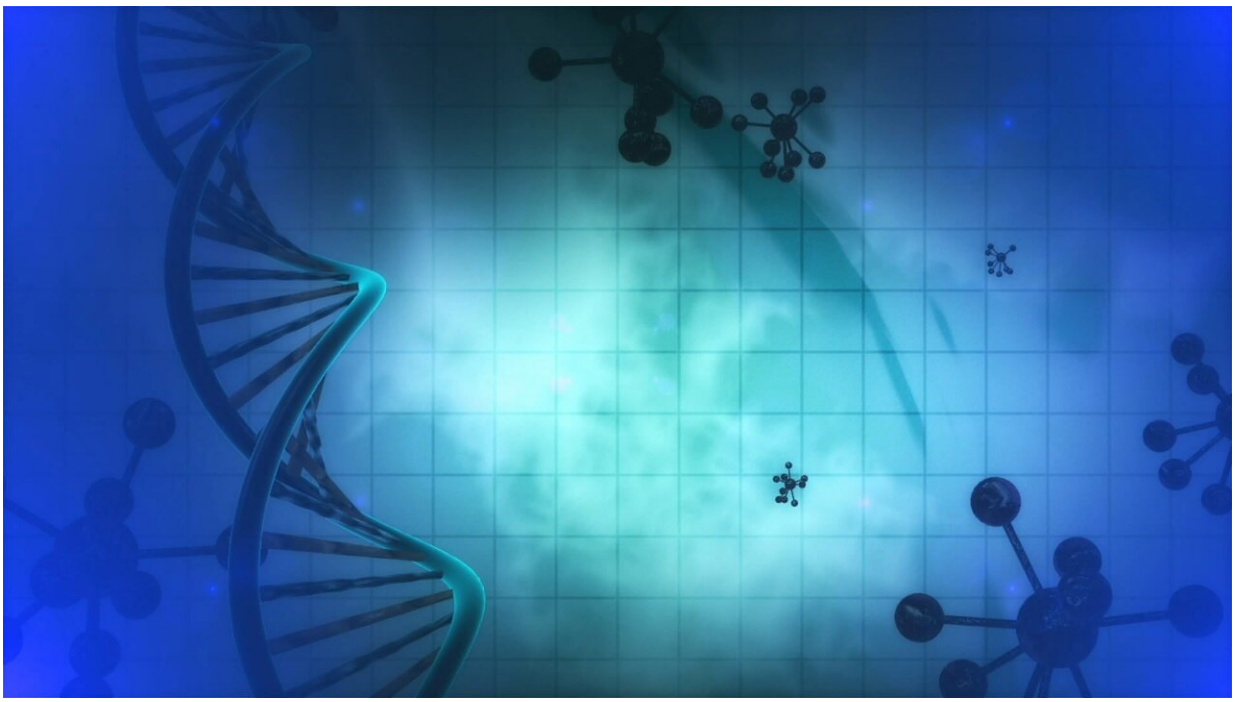

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About one-fifth of often deadly head and neck cancers harbor genetic mutations in a pathway that is key to normal cell growth, and scientists report those mutations, which enable abnormal cancer cell growth, can also make the cancer vulnerable.

Keys to targeting that vulnerability include individualized genomic analysis to identify a patient's specific mutation, and finding the drugs that directly target it, investigations that should be given more attention in cancer therapy development, they report in a review article in the journal *NPJ Genomic Medicine*.

The MAPK pathway is a "signaling hub" for cells important to the usual development of the head and neck region, and activating key pathway constituents, like the genes MAPK1 and HRAS, is known to drive the growth of a variety of cancers, says Dr. Vivian Wai Yan Lui, molecular pharmacologist and translational scientist at the Georgia Cancer Center and Medical College of Georgia and the paper's corresponding author.

But the mutations in the genes in the MAPK pathway that enable tumor growth can also make it sensitive to drug therapy, says Lui. While a lot of discovery is still needed to find more mutations in the MAPK pathway and the drugs that target them, Lui says they are among the most logical treatment targets for this tough-to-treat cancer.

As she speaks, she is looking in her lab for drugs that kill head and neck primary tumors from patients, and at the genetics behind how they kill.

"It's critical to the survival of the cancer," says Lui, and every cancer type likely has one or more drug-sensitizing mutations that may vary in individuals depending on how they got cancer.

If these types of studies continue to find the methodology works, gene panels might need to be developed to expedite target discovery in this very heterogenous cancer, the scientists write.

More clinical trials around the globe at institutions like MCG and the Georgia Cancer Center are essential to identifying these specific mutations and drugs that target them in a precision manner, Lui notes.

Also, next on the horizon is combining this "precision medicine" approach with immunotherapy that better enables a patient's immune system to also target the cancer, she says.

Lui's interest in the MAPK pathway solidified almost a decade ago at the University of Pittsburgh where she did her postdoctoral studies and eventually joined the faculty. Her mentor was Dr. Jennifer R. Grandis (now at the University of California, San Francisco), who led the head and neck cancer program there. The patient in his 30s, a heavy smoker and drinker, had stage four head and neck squamous cell carcinoma that had metastasized to his lymph nodes. The patient went to Pittsburgh for removal of the lymph nodes and the primary tumor but was fortunate enough to be eligible for a "window of opportunity" trial there. Before starting any standard treatment, he received a trial drug for 13 days, in his case an epidermal growth factor receptor, or EGFR, blocker. The receptor is involved in cell growth, and is found on some normal cells, including in the head and neck area where there is a lot of natural cell turnover because of exposure to things like food and drink. However, in cancer cells, including head and neck cancer cells, EGFR is abundantly expressed for the rapid growth critical to a tumor's spread and survival.

The patient was given the drug, erlotinib, which was not known to be particularly effective in these cancers but was being looked at to see if it would quieten signaling of this factor that was important to the cancer's growth. When he went for surgery following the trial, the surgeon called to report there was no cancer on his tongue and studies of his 36 lymph nodes indicated they also now showed no evidence of cancer. The patient was still doing well by the time the Pittsburgh colleagues published the paper two years later in 2015 in *JAMA Oncology*.

His was rightly called an "exceptional response," the first Lui and her colleagues had found in head and neck cancer, and she had to figure out the mutation the drug targeted to enable such a response. Exceptional

responders are how the National Cancer Institute describes people who have more than a six-month response to a therapy when they are running out of treatment options.

An EGFR gene mutation was a logical choice for his mutation. Harvard investigators had previously found that in non-small cell lung cancer, EGFR activating mutations could activate tumor cell growth, which also made tumor cells "addicted" to the signal from the mutated EGFR. The drug erlotinib could break the addiction and inhibit cancer cell growth.

Lui didn't find an EGFR mutation in this young man's pretreatment biopsy but reasoned the mutation had to have something to do with the receptor's signaling network. She was surprised—and the first—to find it was a MAPK1 gene mutation, MAPK1 p.E322K specifically, that could also be found in liver, breast and other cancers.

When they later engineered the mutation in head and neck cancer cells, the already aggressive cells grew even faster, Lui says of a mutation that can result from habits like heavy smoking and drinking. They would also find that the particular mutation was very common in the United States in patients with head and neck cancer, while there was a wider spectrum of mutations present in Asians with the cancer.

Erlotinib had actually failed in clinical trials because it wasn't given to the right patients, which is what precision medicine is, Lui notes. In fact, laboratory studies had indicated that activation of MAPK1 confers resistance to erlotinib, she says, while this patient's response clearly counters that. Follow up work by Grandis indicated that in patients actually, the higher the MAPK1 activation, the better the cancer responded to erlotinib.

To help move cancer treatment forward, Lui encourages physicians who come across these types of "exceptional responses" to report them, work

with scientists to study them, then pursue clinical trials when appropriate.

For patients, her message is not to give up because with more high-level analysis of tumors, there might be a certain mutation that makes their cancer vulnerable to a specific medication, she says of these "gene-drug responses" that are the focal point of her translational work.

"There are secrets that make the cancer vulnerable," Lui says. "When cancer cells have an important gene mutation that they are activating or that cancer cells are addicted to for survival, then when you hit that signaling pathway, the cancer cells will die or be really well controlled."

Prior to the era of genomic medicine, when scientists began to identify and target a specific gene mutation, "non-precision" drug treatment of the MAPK pathway in head and neck cancers as well as other cancers were "futile," and typically "failed miserably" in clinical trials, Lui and her colleagues write.

While the reasons may be uncertain, they likely include the wrong drug for that specific, problematic mutation, Lui says, as well as the fact that some MAPK pathway mutations are known to convey drug resistance.

Either way, there is a lot of work to do. Today there are just a handful of drugs that target specific, cancer-causing mutations in head and neck cancer but there aren't effective precision drugs for about 80% of patients, Lui and her coauthors write.

But there is mounting evidence that targeting specific MAPK pathway mutations in the pathway like MAPK1, HRAS, KRAS and BRAF can be very effective for these patients.

As an example, the RAS inhibitor tipifarnib received Breakthrough

Therapy Designation by the Food and Drug Administration in February 2021 for patients with a specific recurrent or metastatic HRAS-mutant head and neck squamous cell cancer. HRAS is involved in cell growth signaling.

Also, studies indicate that EGFR targeted therapy in metastatic non-small cell lung cancer, increases progression-free survival to a median of 18.9 months and median overall survival beyond three years and reduces death rates about 52%. In 2016 the Food and Drug Administration modified its approval of erlotinib to treat non-small cell lung cancer patients with the specific EGFR mutations. In 2020, the FDA approved erlotinib in combination with ramucirumab, a monoclonal antibody that binds to a receptor for vascular endothelial growth factor, or VEGF, which tumors use to grow the blood vessels they need to thrive, as a frontline treatment for these cancers. The FDA granted Breakthrough Therapy Designation to tipifarnib, an inhibitor of a protein which has the downstream effect of interfering in this case with mutations of the gene HRAS, which is also involved in cell division and in the MAPK pathway. There are now more than 1.5 million people with non-small cell lung cancer on precision medicine because of investigators who continued to examine the initial few responders, Lui says.

Lui is a native of Hong Kong, who was on the faculty of The Chinese University of Hong Kong before joining the MCG faculty in October 2021. In 2020 Lui and her colleagues reported that MAPK pathway mutations are a factor in about one-fifth of head and neck cancer patients and that "unexpectedly" these mutations are associated with longer patient survival than other causes like human papillomavirus.

Head and neck cancer is typically aggressive and often both the disease and its treatment are painful and disfiguring. It carries a higher risk of suicide than many other cancer types. The incidence of head and neck cancer is going up across the world, with causes including tobacco and/or

alcohol use, air pollutants, cancer causing viruses like the sexually transmitted HPV, and Epstein-Barr virus, one of the most common viruses that is primarily spread by saliva and can cause problems like infectious mononucleosis. Other causes include poor dental hygiene and chewing betel nut, a stimulant which comes from the Areca palm plant, and is used as a recreational drug and as a still-unproven treatment for problems like schizophrenia and glaucoma. Chewing betel nut is a common cultural practice in South and Southeast Asia and the Asian Pacific. It's often chewed with products like tobacco and has been associated with cancer and a host of other medical problems like a slow heart rate and stomach ulcers.

The carcinogens largely damage the lining of the head and neck region resulting in one or more mutations that can lead to cancer.

More information: Hoi-Lam Ngan et al, Precision drugging of the MAPK pathway in head and neck cancer, *npj Genomic Medicine* (2022). DOI: 10.1038/s41525-022-00293-1

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