Genetic changes in head and neck cancer, immunotherapy resistance identified

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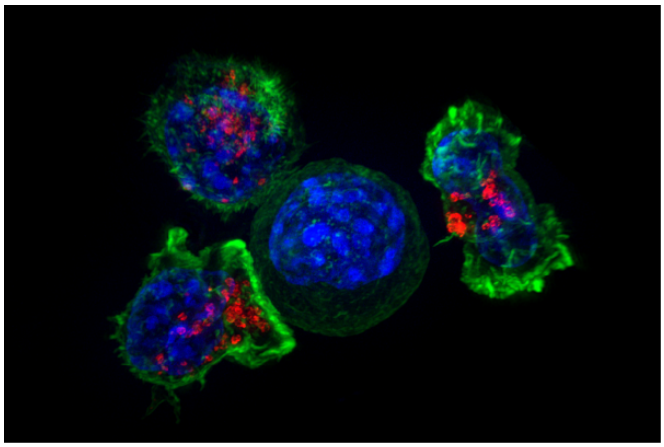

Killer T cells surround a cancer cell. Credit: NIH

A multi-institutional team of researchers has identified both the genetic abnormalities that drive pre-cancer cells into becoming an invasive type of head and neck cancer and patients who are least likely to respond to immunotherapy.

"Through a series of surprises, we followed clues that focused more and more tightly on specific genetic imbalances and their role in the effects of specific immune components in tumor development," said co-principal investigator Webster Cavenee, Ph.D., Distinguished Professor Emeritus at University of California San Diego School of Medicine.

"The genetic abnormalities we identified drive changes in the immune cell composition of the tumors that, in turn, dictates responsiveness to standard of care immune checkpoint inhibitors."

Reporting in the April 26, 2021 online issue of the *Proceedings of the National Academy of Sciences*, researchers describe the role of somatic copy-number alterations—abnormalities that result in the loss or gain in a copy of a gene—and the loss of chromosome 9p in the development of human papillomavirus (HPV)-negative head and neck cancer.

The loss of chromosome 9p and the deletion of JAK2 and PD-LI, two neighboring genes found on chromosome 9p, was associated with resistance to immune checkpoint inhibitors, a type of cancer immunotherapy that uses antibodies to make tumor cells visible to a patient's immune system.

"Although programmed death-1 (PD-1) immune checkpoint inhibitors represent a major breakthrough in cancer treatment, only 15 percent of patients with HPV-negative head and neck cancer respond to treatment," said co-principal investigator Scott M. Lippman, MD, senior associate dean, associate vice chancellor for cancer research and care and Chugai Pharmaceutical Chair in Cancer at UC San Diego School of Medicine.

"The ability to predict a patient's response or resistance to this class of therapies, a major unmet clinical need, is a unique and novel discovery. Knowing who will not respond avoids losing several months to ineffective therapy with huge financial costs and impacts to quality of life," said Lippman, director of UC San Diego Moores Cancer Center and medical oncologist who specializes in the treatment of patients with head and neck cancer at UC San Diego Health, San Diego's only National Cancer Institute-designated comprehensive cancer center.

For this study, co-led by New York University Langone Health's Teresa Davoli, Ph.D., and The University of Texas MD Anderson Cancer Center's William N. William, MD, with co-investigator Steve Dubinett, MD, of UCLA Jonsson Comprehensive Cancer Center, researchers prospectively followed 188 patients at MD Anderson Cancer Center to study genomic and immune drivers of the transition to invasive HPV-negative head and neck cancer.

They reviewed comprehensive genomic and transcriptomic data of 343 HPV-negative head and neck cancer patients from The Cancer Genome Atlas and 32 HPV-negative head and neck cancer cell lines from the Cancer Cell Line Encyclopedia project, and analyzed patient survival after immunotherapy in real-world evidence cohort data from Caris Life Sciences.

In 2021, the National Cancer Institute estimates approximately 54,000 new cases of head and neck cancers will be diagnosed in the United States, with 10,850 deaths. HPV-negative head squamous cell carcinomas are the most common, increasing and lethal subtype of this malignancy worldwide, said Lippman.

"The data serves as a powerful predictive marker, transforming standard of care for precision immunotherapy for patients with advanced, recurrent head and neck cancer," said Lippman. "And, while we focused in an unprecedented extensive interrogation of the most globally lethal form of head and neck squamous cancer, accounting for more than 300,000 deaths annually, the application may be useful in a wide variety of solid tumors for which immune checkpoint inhibitors comprises standard of care."

More information: William N. William el al., "Immune evasion in HPV? head and neck precancer–cancer transition is driven by an aneuploid switch involving chromosome 9p loss," *PNAS* (2021). www.pnas.org/cgi/doi/10.1073/pnas.2022655118

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