Absent p53, oral cancers recruit and reprogram nerves to fuel tumor growth

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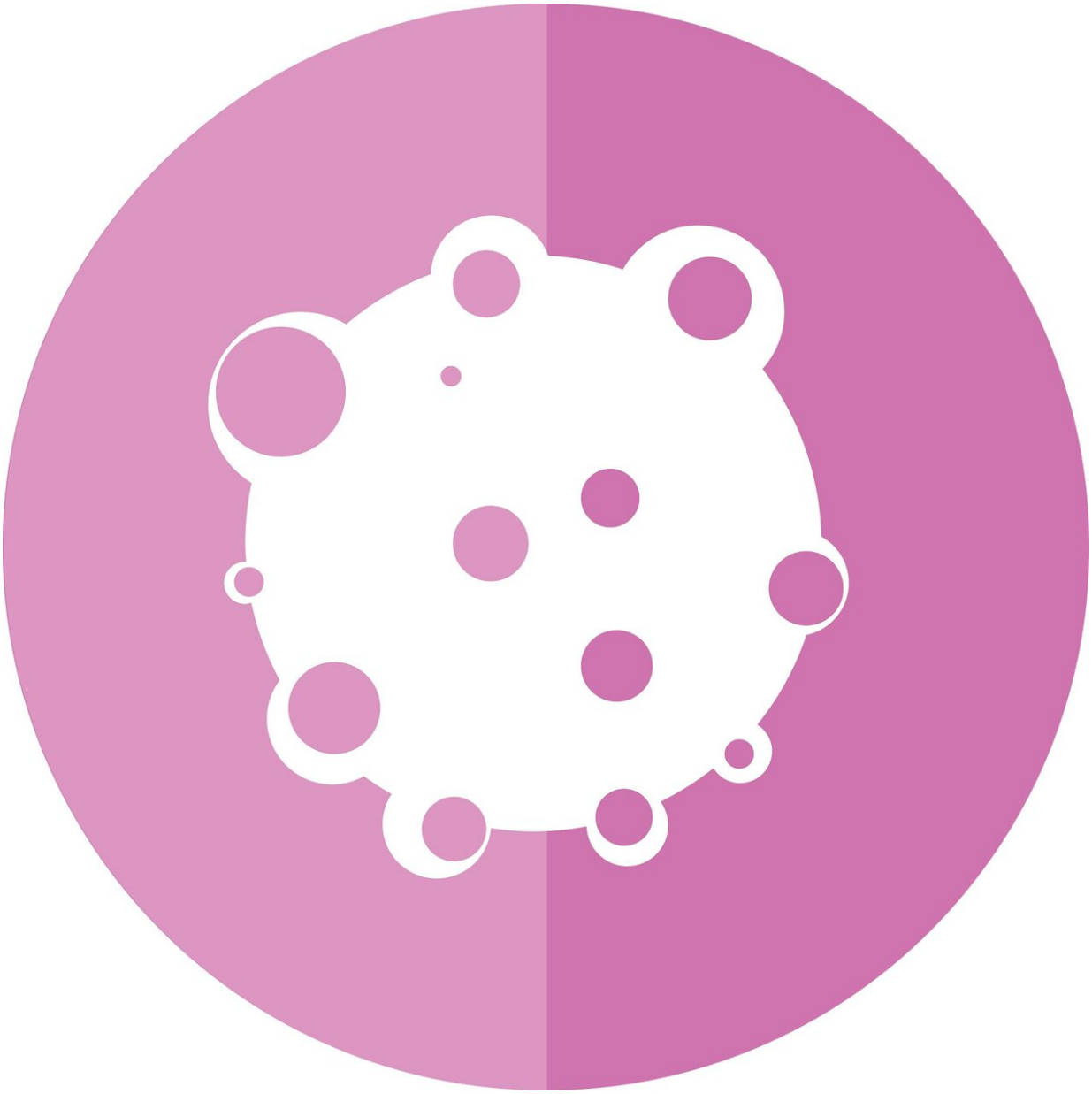

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Loss of an important tumor-suppressing gene allows head and neck cancer to spin off signals to nearby nerves, changing their function and recruiting them to the tumor, where they fuel growth and cancer progression, researchers from The University of Texas MD Anderson Cancer Center report in the journal *Nature* today.

By cracking the mechanism that launches neuronal invasion of tumors, a known marker of poor prognosis for patients, the team has uncovered possible avenues to block the process, including the use of drugs commonly used to treat blood pressure and irregular heartbeat.

"Tons of studies show that patients who have lots of nerves in their tumor are doing worse—recurrence rates are higher, survival is shorter," says co-first author Moran Amit, M.D., Ph.D., assistant professor of Head and Neck Surgery. "Nerve endings found in surgically removed tumors can't be easily characterized or tracked back to their source, so it's been a neglected field, a neglected hallmark of cancer."

"When surgeons remove head and neck cancers and find a high degree of nerve invasion, post-surgical radiation sometimes is effective," said co-senior author Jeffrey Myers, M.D., Ph.D., chair of Head and Neck Surgery. "But we really haven't understood whether the tumor was growing into the nerves or the nerve growing into the tumor and what signaling drove those interactions."

Co-senior author George Calin, M.D., Ph.D., professor of Experimental Therapeutics and an expert on non-coding RNAs added that the paper "puts together for the first time the mechanism of involvement of neurons in tumor generation, a new hallmark of cancer."

The team found that the neurons that invade the tumor are adrenergic nerves, which are involved in stress response. These nerves' neurotransmitters—adrenaline (epinephrine) and noradrenaline (norepinephrine) - are susceptible to drugs known as alpha and beta blockers, long used to treat high blood pressure and irregular heartbeats.

In the study, mice with oral cancer treated with the adrenergic blocker carvedilol had sharply lower tumor growth and cancer cell proliferation. Myers says the team is working to develop clinical trials of adrenergic blockers, most likely in combination with other drugs.

"We used to think that nerves are just randomly growing into the tumor, and that's completely wrong," Amit says.

Loss of p53 flips a microRNA switch to re-program neurons

Damage to the p53 gene is a major characteristic of head and neck cancers. A tumor-suppressing master transcriptional gene that governs the expression of many other genes, p53 is also mutated in a variety of cancers.

The team found high density of neurons in p53-deficient mouse models and human xenograft tumors of oral cavity squamous cell carcinoma (OCSCC) as well as increased neural growth in clusters of nerves exposed to p53-deficient OCSCC.

The researchers also discovered that oral cancer communicates with nerves by launching extracellular vesicles—membrane balls that carry various molecules—packed with microRNAs to connect with the nerves. The miRNA cargo varied depending on p53 status of the tumors.

"When you have intact p53, you have specific types of microRNAs that keep neurons in a quiescent state," Amit says. "Once you lose p53, the micro RNA population within the exosomes changes and then you get positive signals to induce nerve growth."

Investigators identified adrenergic nerves extending into the tumors and suspected they were extensions of pre-existing nerves. However, when they cut adrenergic nerves before inducing tumors in mice, adrenergic nerves still appeared in the tumor and the tumors still grew.

Subsequent experiments showed the miRNAs in vesicles from p53-deficient tumors were connecting instead with existing sensory nerves, a different nerve type, and actually changing them into the adrenergic type. These neo-adrenergic nerves then invaded the tumor.

To confirm this finding, they cut sensory nerves ahead of inducing p53-deficient tumors in mice. Without the sensory nerve targets for the vesicles, the tumor shrank.

Impact of adrenergic nerve density on patients

To validate the impact of their findings on people with OCSCC, the researchers analyzed the presence of adrenergic nerves in the tumors of 70 patients who were treated at MD Anderson. Adrenergic nerve density in the tumors was associated with lower recurrence-free survival and overall survival.

The statistical significance of the adrenergic nerve densities held up in multivariable analysis after adjustment for other variables, such as age, sex, cancer stage, surgical margin status, overall neuronal invasion and treatment type. They suggest nerve density measurements merit exploration as a predictive marker of oral cancer aggressiveness. Myers, Calin, Amit and colleagues believe the paper opens up a new area for

cancer researchers.

"Neurons control everything that we do in everyday life," Amit says. "They control our voluntary and involuntary bodily functions, so it's intuitive that they are involved in cancer."

More information: Loss of p53 drives neuron reprogramming in head and neck cancer, *Nature* (2020). DOI: 10.1038/s41586-020-1996-3 , nature.com/articles/s41586-020-1996-3

Provided by University of Texas M. D. Anderson Cancer Center

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