PRESS RELEASE

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Tumor Suppressor Gene Mutations Trigger Immune Activation in Early Oral Cancer

Researchers found that imbalanced p53–RB signaling activates cGAS–STING-mediated immunity, delaying oral cancer progression

Genetic alterations in *TP53* and *CDKN2A* can shape the immune response during early oral cancer development. Researchers from Tokushima University reveal that imbalanced p53–RB signaling activated the cGAS–STING pathway, allowing increased inflammatory signaling and infiltration of cytotoxic T cells and natural killer cells. This immune response was associated with delayed progression to invasive oral cancer. The findings highlight how specific tumor-suppressor alterations can influence antitumor immunity and progression during early carcinogenesis.

Head and neck squamous cell carcinoma (HNSCC) frequently develops in the oral and upper aerodigestive regions following chronic exposure to mutagenic factors such as tobacco, alcohol, and betel nut. Alterations in the tumor suppressor genes *TP53* and *CDKN2A* are among the most common genetic changes in HNSCC and often occur together in the same tumor. However, the consequences of these combined alterations during the early stages of oral carcinogenesis remain poorly understood.

To better understand this, a research team comprising Ph.D. student Zichao Lu, Associate Professor Yasuhiro Mouri, and Professor Yasusei Kudo from the Department of Oral Bioscience, Tokushima University Graduate School of Biomedical Sciences, Japan, and the Institute of Photonics Human Health Frontier, Tokushima University, investigated how different combinations of *TP53* and *CDKN2A* alterations influence oral carcinogenesis and the surrounding immune microenvironment. Their findings were made available online on August 15, 2026, and published in Volume 45 of the journal *Oncogene* on October 20, 2026.

The researchers were motivated by limitations in conventional mouse models of oral cancer. Although *TP53* and *CDKN2A* are frequently altered together in human HNSCC, conventional mouse models in which both genes are completely inactivated have not adequately reproduced oral carcinogenesis. Moreover, the functions of these genes are not always completely lost in human tumors, as partial activity may remain depending on the type and combination of mutations. The team therefore aimed to develop a model that more closely reflects these genetic conditions in human HNSCC.

The team generated mice carrying a human-relevant *CDKN2A* R80X truncating mutation and combined it with a loss-of-function alteration in *Trp53*, the mouse counterpart of *TP53*. The mice were then exposed to 4-nitroquinoline-1-oxide, a carcinogen widely used to model oral cancer

development. This experimental system allowed the team to examine how specific combinations of tumor suppressor alterations affect the oral epithelium under carcinogenic stress.

The results revealed a distinct immune response during the early stages of carcinogenesis. Mice carrying the relevant combination of *Trp53* and *Cdkn2a* alterations showed activation of the cGAS–STING–NF-κB axis, accompanied by increased expression of inflammatory cytokines, chemokines, and interferon-stimulated genes. Together, these changes indicated that the altered tumor-suppressor signaling was linked to activation of innate immune responses in the oral epithelium.

The immune response was also reflected in the cellular environment surrounding the developing lesions. The researchers observed increased infiltration of T cells and natural killer cells, with a higher ratio of cytotoxic T cells to regulatory T cells. Chemokines including Ccl3, Ccl4, and Ccl20 were elevated, further supporting the recruitment of cytotoxic immune cells. The authors explain, *"Our study reveals that the combination of genetic alterations in TP53 and CDKN2A can shape the immune microenvironment during the early stages of oral carcinogenesis."*

This immune activation was associated with delayed progression to invasive oral cancer. In addition, treatment with the STING inhibitor H-151 reduced interferon-related gene expression and decreased the infiltration of certain T-cell populations, providing functional evidence that STING signaling contributes to the observed immune response.

"Tumor-suppressor alterations do not simply promote cancer development; specific combinations of these alterations can also activate antitumor immunity during early carcinogenesis," the authors state.

The immune landscape changed as the tumors progressed. As lesions developed into squamous cell carcinoma, T-cell infiltration generally decreased across genotypes, consistent with the emergence of a more immunosuppressive tumor microenvironment. The findings therefore suggest that the immune activation associated with specific *TP53* and *CDKN2A* combinations may be a feature of early carcinogenesis that changes as malignancy develops.

To examine whether these genetic interactions were also associated with clinical outcomes in humans, the researchers analyzed data from The Cancer Genome Atlas HNSC cohort. Combined *TP53/CDKN2A* alteration patterns significantly separated overall survival and were associated with distinct survival patterns. However, immune-activation signatures observed in the early mouse model were not clearly detected in the predominantly advanced-stage human tumors analyzed, potentially reflecting the later stage of disease represented in these samples.

Looking ahead, the findings could have implications for assessing oral potentially malignant lesions. Combining *TP53* and *CDKN2A* genetic status with the immune status of oral lesions may eventually help assess progression risk and identify patients who require closer surveillance or earlier intervention. The findings may also provide a basis for investigating approaches targeting the cGAS–STING pathway or immune checkpoints according to the genetic and immune

characteristics of individual tumors. However, further studies are needed to determine the optimal timing and clinical effectiveness of these approaches in humans.

"Ultimately, this knowledge may contribute to more precise risk assessment of oral precancerous lesions and to personalized prevention and treatment strategies based on both genetic alterations and the tumor immune microenvironment," the authors conclude.

Together, the findings provide a new framework for understanding tumor-suppressor alterations not simply as functional or non-functional, but as specific combinations of changes that can influence immune responses during the earliest stages of oral cancer development.

Reference

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About Tokushima University

Tokushima University, established in 1949, is a leading national university in the city of Tokushima, Japan. It is organized into six graduate schools and undergraduate faculties. It has been working to further strengthen its education, research, and social contributions in order to make greater advancements that solve global issues while aligning with the UN Sustainable Development Goals (SDGs) from a regional standpoint. The university collaborates with other educational institutes and industries to foster an environment that nurtures future academicians, researchers, and entrepreneurs who have the potential to make the world a better place.

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About Zichao Lu from Tokushima University

Zichao Lu is a Ph.D. student at Tokushima University, Japan, affiliated with the Department of Oral Bioscience, Tokushima University Graduate School of Biomedical Sciences, and the Institute of Photonics Human Health Frontier. Lu's research focuses on oral cancer biology, with work on the genetic and immune mechanisms underlying early oral cancer development. Lu is the first author of a 2026 study published in *Oncogene* investigating how imbalanced p53–RB signaling activates cGAS–STING-mediated immune responses during early oral carcinogenesis. In August 2026, Lu obtained a degree from Tokushima University and was scheduled to begin work as a resident in China in September 2026.

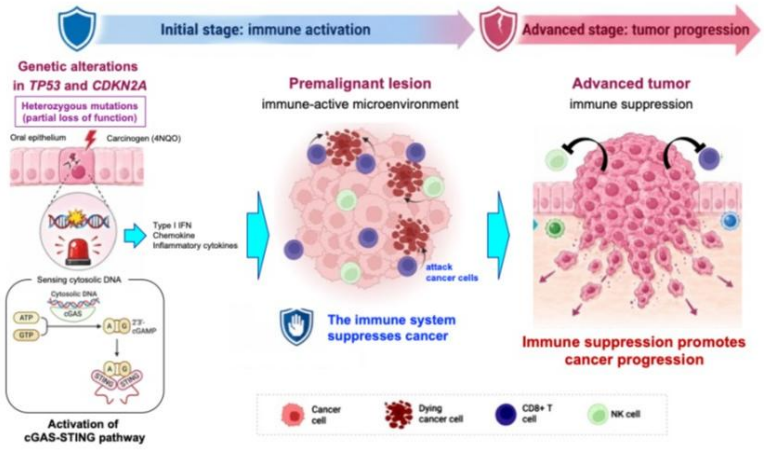
About Professor Yasusei Kudo from Tokushima University
Dr. Yasusei Kudo is a Professor in the Department of Oral Bioscience at Tokushima University Graduate School of Biomedical Sciences, Japan, and a distinguished Principal Investigator at the Institute of Photonics Human Health Frontier, Tokushima University, Japan. He earned his Bachelor's degree in Dentistry and Ph.D. from Hiroshima University. With more than 27 years of research experience, Dr. Kudo has authored more than 270 publications. His research focuses on oral cancer pathogenesis, cancer cell proliferation, invasion and metastasis, cell signaling, ubiquitin-mediated proteolysis, and molecular pharmacology. His achievements include multiple research and mentoring awards, including the Japanese Society of Pathology's awards.

About Associate Professor Yasuhiro Mouri from Tokushima University
Dr. Yasuhiro Mouri is an Associate Professor in the Department of Oral Bioscience at Tokushima University Graduate School of Biomedical Sciences, Japan, and is also affiliated with the Institute of Photonics Human Health Frontier, Tokushima University. He earned his Ph.D. in Medical Science from Tokushima University in 2011. His research focuses on oral biology and immunology, including the molecular mechanisms underlying oral cancer and related diseases. He has authored numerous research publications in these fields.

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Image



Title: How a combination of genetic alterations triggers antitumor immunity during early oral carcinogenesis
Caption: In mice carrying heterozygous mutations in both *Trp53* and *Cdkn2a*, the DNA-sensing cGAS–STING pathway is activated in epithelial cells during the early stages of oral carcinogenesis induced by the mutagen 4NQO. This activation induces antitumor immunity and is associated with a relative delay in progression to invasive cancer. As tumors progress, however, antitumor immune cells, including $CD8^+$ T cells and NK cells, decrease and the tumors become more aggressive.
Credit: Associate Professor Yasuhiro Mouri and Professor Yasusei Kudo from Tokushima University, Japan
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