Proteogenomics offers insight to treating head and neck squamous cell carcinoma

January 7 2021

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Proteogenomic analysis may offer new insight into matching cancer patients with an effective therapy for their particular cancer. A new study identifies three molecular subtypes in head and neck squamous cell carcinoma (HNSCC) that could be used to better determine appropriate treatment. The research led by Baylor College of Medicine, Johns Hopkins University and the National Cancer Institute's Clinical

Proteomic Tumor Analysis Consortium (CPTAC) is published in the journal *Cancer Cell.*

Researchers profiled proteins, phosphosites and signaling pathways in 108 human papillomavirus-negative HNSCC tumors in order to understand how genetic aberrations drive tumor behavior and response to therapies. Currently, there are a few FDA-approved therapies for HNSCC, including an epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) inhibitor and two PD-1 inhibitors, but response rates are moderate. In this study, researchers aimed to find out why certain patients respond to certain treatments to better match the patient to an appropriate course of treatment.

"We found three subtypes of head and neck [squamous cell carcinoma](link), and each subtype may be good candidates for a different type of therapy—EGFR inhibitors, CDK inhibitors or immunotherapy," said Dr. Bing Zhang, lead contact of the study and professor in the Lester and Sue Smith Breast Center and the Department of Molecular and Human Genetics at Baylor. "We also identified candidate biomarkers that could be used to match patients to effective therapies or clinical trials."

Finding effective biomarkers

One important finding involved matching HNSCC patients to EGFR mAb inhibitors. Cetuximab, an EGFR mAb medication, was approved by the FDA in 2006 as the first targeted therapy for HNSCC, however the success rate for this treatment is low. Moreover, EGFR amplification or overexpression cannot predict response to EGFR mAbs. In this study, researchers found that EGFR ligands, instead of EGFR itself, act as the limiting factor for EGFR pathway activation. When ligand is low, the downstream pathway will not be triggered, even if EGFR protein is highly overexpressed.

"We proposed that the EGFR ligand should be used as a biomarker, rather than EGFR amplification or overexpression, to help select patients for the EGFR monoclonal antibody treatment," said Zhang, a member of the Dan L Duncan Comprehensive Cancer Center, a Cancer Prevention & Research Institute of Texas (CPRIT) Scholar and a McNair Scholar at Baylor. "Tumors with high EGFR amplification do not necessarily have high levels of EGFR ligands, which may underlie their lack of response to EGFR mAb therapy." The team confirmed this hypothesis by analyzing previously published data from patient-derived xenograft models and a clinical trial.

Additionally, tracking a key tumor suppressor known as Rb (retinoblastoma), the research team identified a striking finding that suggests that Rb phosphorylation status could potentially be a better indicator of a patient's response to CDK4/6 inhibitor therapy. The study showed that the many mutations in the genes regulating CDK4/6 activity were neither necessary nor sufficient for activation of CDK4/6. The team found that the CDK4 activity was best measured through Rb phosphorylation measurements, thus identifying a potential measure for patient selection in CDK inhibitor clinical trials.

Immunotherapy insights

The research team also found important insights into the effectiveness of immunotherapy. PD-1 inhibitors target the interaction between immune checkpoints PD-1 and PD-L1, but success rates of immunotherapy are low, even when PD-L1 expression is used for patient selection. The researchers examined tumors with high expression of PD-L1 and found that when a tumor overexpresses PD-L1, it also upregulates other immune checkpoints, thus allowing the tumor growth despite the use of PD-1 inhibitors. This observation suggests that PD-1 and PD-L1 activated tumors with hot immune environments may require multiple types of immunotherapy, which target different immune checkpoint

proteins, to be effective.

Conversely, tumors with cold immune environments are not good targets for immunotherapy. Examination of how a tumor becomes immune-cold tumor showed that the problem stems from a flaw in its antigen presentation pathway where multiple key gene components of the antigen presentation pathway were deleted. As a result, although tumor antigens are being expressed, the immune system is not able to recognize them on the surface of the cell and therefore fail to activate the body's defense system against the tumor. These deletions have the potential to be effective targets for future therapies.

"This study extends our biological understanding of HPV-negative HNSCCs and generates therapeutic hypotheses that may serve as the basis for future studies and clinical trials toward molecularly-guided precision medicine treatment of this aggressive cancer type," said Dr. Daniel W. Chan, co-corresponding author of the study, professor of pathology and oncology, and director of the Center for Biomarker Discovery and Translation at the Johns Hopkins University School of Medicine.

  More information: Chen Huang et al. Proteogenomic insights into the biology and treatment of HPV-negative head and neck squamous cell carcinoma. *Cancer Cell.* DOI: doi.org/10.1016/j.ccell.2020.12.007

  Provided by Baylor College of Medicine