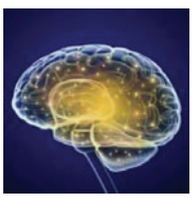
Cancer Research
Breaking Insights
Highlights from Recent Cancer Literature
AACR
American Association for Cancer Research

Proteomic Profiling of Medulloblastoma



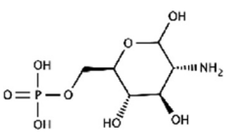
Medulloblastoma is the most common malignant pediatric brain tumor. Using genomic and epigenomic analyses, medulloblastoma has been classified into four main subgroups (wingless, Sonic hedgehog, group 3, and group 4), however, proteomic analysis is lacking. Forget and colleagues (1) and Archer and colleagues (2) performed proteomic and phosphoproteomic analyses across 41 and 45 primary medulloblastoma samples. Both studies showed similar levels of heterogeneity at the protein level and could recapitulate the four established tumor subgroups. Forget and colleagues focused on Group 4, showed aberrant activity of the ERBB4-SRC signaling axis, and generated a murine model of SRC activation, the first bona fide sporadic Group 4 model. Archer and colleagues focused on aggressive MYC-amplified Group 3 medulloblastoma. Using proteomics, they were able to stratify patients robustly and identified the DNA-dependent protein kinase (PRKDC) as strongly associated with the most aggressive forms of Group 3.

Expert Commentary: These studies leveraged proteomic profiling to identify novel promising targets for the most common and aggressive forms of medulloblastoma.

1. Forget A, Martignetti L, Puget S, Calzone L, Brabetz S, Picard D, et al. Aberrant ERBB4-SRC signaling as a hallmark of group 4 medulloblastoma revealed by integrative phosphoproteomic profiling. Cancer Cell 2018;34:379–95.e7.

2. Archer TC, Ehrenberger T, Mundt F, Gold MP, Krug K, Mah CK, et al. Proteomics, post-translational modifications, and integrative analyses reveal molecular heterogeneity within medulloblastoma subgroups. Cancer Cell 2018;34:396–410.e8.

O-GlcNAcylation Drives *Kras*-Induced Lung Tumorigenesis

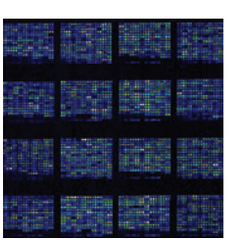


Kras tumorigenesis requires suppression of oncogene-induced senescence (OIS). Epithelial-mesenchymal transition transcription factors (EMT-TF) can suppress *Kras*-induced senescence. Taparra and colleagues demonstrate that EMT-TFs suppress OIS and contribute to lung tumorigenesis by promoting metabolic reprogramming via the hexosamine biosynthetic pathway (HBP), and increased protein posttranslational modification by O-GlcNAcylation. In novel autochthonous mouse models, genetic or pharmacologic targeting of the HBP or O-GlcNAcylation induced senescence and delayed $Kras^{G12D}$ lung tumorigenesis *in vitro* and *in vivo*. Specific O-GlcNAcylation of c-Myc correlated with this novel EMT-HBP axis and accelerated lung tumorigenesis.

Expert Commentary: This study describes a novel role for an EMT-HBP axis in mediating suppression of OIS and *Kras* tumorigenesis and suggests potential novel therapeutic targets for *Kras* mutant lung cancer. *(Image courtesy of Wikimedia Commons.)*

Taparra K, Wang H, Malek R, Lafargue A, Barbhuiya MA, Wang X, et al. O-GlcNAcylation is required for mutant KRAS-induced lung tumorigenesis. The Journal of Clinical Investigation; Published online August 21, 2018; doi: 10.1172/JCI94844.

3D Reconstruction of the Immune Tumor Microenvironment



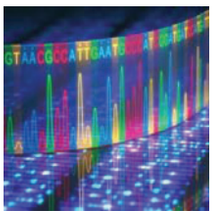
Dissecting the tumor-immune landscape would yield valuable prognostic information in triple-negative breast cancers and other cancer types. Keren and colleagues employ a novel high-powered immunohistochemistry-like technology called multiplexed ion beam imaging by time-of-flight (MIBI-TOF) to measure expression of 36 proteins simultaneously on formalin-fixed tissue sections from triple-negative breast cancers. Two patterns of spatial organization were observed, mixed and compartmentalized. Mixed tumors showed immune cells diffusely mixed throughout tumors and high PD-1 expression on $CD8^+$ T cells, with PD-L1 on the tumor cells. Compartmentalized tumors had separate areas of immune cells and tumor cells and exhibited high expression of PD-1 on $CD4^+$ T cells, with PD-L1 also on immune cells. Compartmentalized spatial organization was associated with better survival.

Expert Commentary: The use of MIBI-TOF allows for assessing archival formalin-fixed paraffin-embedded tumor samples with multiparameter analysis akin to flow cytometry, while retaining spatial resolution.

Keren L, Bosse M, Marquez D, Angoshtari R, Jain S, Varma S, et al. A structured tumor-immune microenvironment in triple negative breast cancer revealed by multiplexed ion beam imaging. Cell 2018;174;1373–87.e19.

Breaking Insights

Genomic Alterations in Endocrine-Resistant Breast Cancers



Mutations in the estrogen receptor gene *ESR1* are found in 18% of endocrine-resistant breast cancers. In the remainder of patients, mechanisms of resistance are largely unknown. Razavi and colleagues carried out a large-scale genomic analysis of hormone receptor-positive breast tumors to identify potential genomic alterations involved in resistance. They identified known or presumed oncogenic mutations in one of the multiple effectors of the MAPK pathway in 13% of hormonal therapy-resistant tumors, with another 9% having mutations in the estrogen receptor transcriptional program. These were mutually exclusive with *ESR1* mutations, suggesting distinct mechanisms of resistance.

Expert Commentary: Understanding the genomic landscape of tumors exposed to systemic therapies can guide future treatment options. Many alterations identified in this study are targetable and could lead to new treatment options.

Razavi P, Chang MT, Xu G, Bandlamudi C, Ross DS, Vasan N, et al. The genomic landscape of endocrine-resistant advanced breast cancers. Cancer Cell 2018;34:427–38.e6.

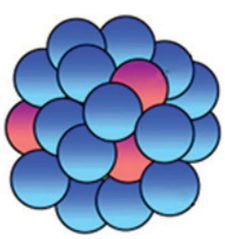
Intronic Polyadenylation as a Cancer Driver

Recent studies have shown that certain alterations in mRNA processing can promote tumorigenesis. Using a 3′-end sequencing method, Lee and colleagues identified widespread intronic polyadenylation (IPA) that produced truncated mRNAs in chronic lymphocytic leukemia (CLL), leading to shortened, yet stable, protein products. IPA-generated truncated proteins lacked tumor suppressor functions of their full-length counterparts (reduced expression of functional tumor-suppressors DICER and FOXN3) or functioned in a dominant-negative manner (derepression of oncogenic targets MYC and PIM2). This technique also identified novel tumor suppressor candidates in CLL corresponding to tumor suppressors mutated at the DNA level in solid tumors.

Expert commentary: While IPA-generated proteins in healthy cells contribute to proteome diversity, CLL-IPAs produce dysfunctional proteins that can perform oncogenic functions similar to or greater than their DNA-mutated counterparts. These findings provide a rationale to explore mRNA modifications that function as cancer drivers.

Lee SH, Singh I, Tisdale S, Abdel-Wahab O, Leslie CS, Mayr C. Widespread intronic polyadenylation inactivates tumour suppressor genes in leukaemia. Nature 2018;56:127–31.

GPNMB Induces Stemness in Dormant Breast Cancer Cells



Type I transmembrane glycoprotein nmb (GPNMB) contributes to breast cancer through epithelial-mesenchymal transition (EMT). Using three-dimensional (3D) sphere culture, Chen and colleagues demonstrated higher expression of cancer stem cells (CSC) and EMT-inducing transcription factor (EMT-TF) genes compared with 2D cultures, and induced cell surface expression of GPNMB on a limited subset of cells in the 3D (but not 2D) cultures. GPNMB^{high} cells expressed high levels of CSCs and EMT-TF genes, had higher sphere-forming frequencies than the GPNMB^{low} cells, and showed undetectable levels of proliferation marker genes.

Expert Commentary: Cell surface expression of GPNMB induces stem cell-like properties in dormant breast cancer cells. Targeting GPNMB could represent an effective cancer treatment. *(Image from cited article courtesy of publisher.)*

Chen C, Okita Y, Watanabe Y, Abe F, Fikry MA, Ichikawa Y, et al. Glycoprotein nmb is exposed on the surface of dormant breast cancer cells and induces stem cell-like properties. Cancer Research; Published first September 17, 2018; doi: 10.1158/0008-5472.CAN-18–0599.

Note: Breaking Insights are written by *Cancer Research* editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.

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Cancer Res 2018;78:6029-6030.