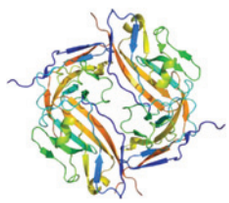
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
AACR American Association for Cancer Research

Blocking the "Don't Eat Me" Signal in Pediatric Brain Tumors



Gholamin and colleagues treated malignant pediatric brain tumor models with a humanized anti-CD47 antibody (Hu59-G4). In primary and metastatic high-risk medulloblastoma, Hu5F9-G4 inhibited growth *in vivo*, including CD15-positive putative medulloblastoma stem cells. Because children with group 3 medulloblastoma die primarily from leptomeningeal metastases, the authors treated the leptomeninges with continuous intraventricular infusion of Hu5F9-G4, observing robust activity. Neither viability nor proliferation rate of normal neural stem cells was affected. They also evaluated Hu5F9-G4 in pediatric ATRT, PNET, pediatric GBM, and DIPG, again demonstrating robust activity against each. Finally, they evaluated Hu5F9-G4 in an immunocompetent model of mouse high-grade glioma, confirming both efficacy and minimal toxicity against the developing nervous system. These results suggest anti-CD47 therapy as a promising strategy across a variety of pediatric brain tumors. *(Image courtesy of Wikimedia Commons.)*

Gholamin S, Mitra SS, Feroze AH, Liu J, Kahn SA, Zhang M, et al. Disrupting the CD47-SIRPα anti-phagocytic axis by a humanized anti-CD47 antibody is an efficacious treatment for malignant pediatric brain tumors. Sci Transl Med 2017;9. doi: 10.1126/scitranslmed.aaf2968.

Bad Luck Hypothesis Revisited

Tomasetti and colleagues earlier reported that most mutations driving cancer arise from replicative errors during division of stem cells from appropriate tissues of origin. This 2015 "bad luck hypothesis" was criticized for using a US-based discovery cohort with homogenous environmental exposures. Tomasetti and colleagues analyzed 17 cancer types across 69 countries, totaling 4.8 billion individuals. They again report a significant correlation with lifetime stem cell divisions. Pairing cancer genome-wide and exome sequencing to epidemiological data, they conclude that most driver mutations arise from replicative errors during stem cell division and not from heredity or environmental exposures. They stress that these data neither eliminate the importance of heredity/environmental exposures nor negate the importance of cancer prevention. However, their data suggest that some cancer types cannot be prevented. For these, early detection is central. *(Image courtesy of Wikimedia Commons.)*

Tomasetti C, Li L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. Science 2017;355:1330–4.

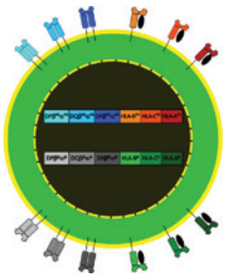
SHANKs Suppress Rap1-Driven Migration and Invasion

In breast and prostate cancer, elevated activity of small G-protein Rap1 correlates with increased cell motility, metastasis, and poor prognosis. Rap1 activates integrins via the well-established Rap1-RIAM-talin axis, and some cancers activate RAP through reduced expression of the Rap1 antagonist Rap1GAP. Lilja and colleagues demonstrate that the scaffold proteins SHANK1 and SHANK3 inhibit integrin activity across cancer types. Mechanistically, SHANKs sequester active Rap1 and R-Ras in cancer cells, limiting their integrin-dependent functions. Based on protein crystallography, they identified a novel RAS-association domain in SHANK1 and SHANK3 proteins. This RAS-association domain was both necessary and sufficient to bind active small G-proteins of the Rap and Ras superfamilies. Thus, SHANK1 and SHANK3, large scaffold proteins linked to actin regulation and autism-like disorders, suppress tumors by attenuating R-Ras– and Rap1-induced cancer cell migration and invasion. *(Image courtesy of Wikimedia Commons.)*

Lilja J, Zacharchenko T, Georgiadou M, Jacquemet G, Franceschi N, Peuhu E, et al. SHANK proteins limit integrin activation by directly interacting with Rap1 and R-Ras. Nat Cell Biol 2017;19:292–305.

Breaking Advances

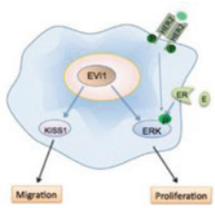
Neoantigens in Lymphoma



Khodadoust and colleagues profiled major histocompatibility complex (MHC) antigen repertoires using LC-MS/MS proteomics from 17 primary patient mantle-cell lymphomas (MCL) to discover potential neoantigens. MHC class I and class II presentation was biased significantly towards abundant proteins. Moreover, while 46% of genes bearing coding mutations, including those known to be recurrently mutated in MCL, had at least one peptide presented, surprisingly these peptides were derived from nonmutated regions of these genes. Instead, all neoantigen peptides were derived exclusively from the lymphoma immunoglobulin heavy- and light-chain variable regions. Khodadoust and colleagues further showed that circulating $CD4^+$ T cells specific for immunoglobulin-derived neoantigens could mediate killing of autologous lymphoma cells. This study demonstrates the utility of an integrative approach combining MHC isolation, peptide identification, and exome sequencing as a platform to uncover tumor neoantigens. *(Image courtesy of Wikimedia Commons.)*

Khodadoust MS, Olsson N, Wager LE, Haabeth OA, Chen B, Swaminathan K, et al. Antigen presentation profiling reveals recognition of lymphoma immunoglobulin neoantigens. Nature 2017;543:723–7.

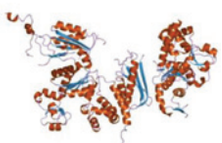
Relevance of EVI1 in ER- and HER2-Negative Breast Cancer



EVI1 is overexpressed in both estrogen receptor-positive and estrogen receptor-negative breast carcinomas, correlating inversely with survival in triple-negative but not in HER2 positive tumors. Wang and colleagues show that silencing expression of EVI1 reduced proliferation, apoptosis resistance, and tumorigenicity of breast cancer cells. Introduction of estrogen rescued these effects in ER^+ breast carcinoma cells and also restored ERK phosphorylation, indicating that EVI1 and estradiol signaling merge in MAPK activation. Silencing EVI1 expression in $HER2^+$ breast cancer cells had no effect on constitutive ERK activity. The authors also demonstrated that G-protein-coupled receptors (GPR) signaled downstream of EVI1. GRP54-ligand KISS1 was a direct transcriptional target of EVI1, facilitating cell migration. Thus, EVI1 mediates oncogenic attributes of ER- and HER2-negative subgroups of breast cancer. *(Image from cited article courtesy of the publisher.)*

Wang, H, Schaefer T, Konantz M, Braun M, Varga Z, Paczulla AM, et al. Prominent oncogenic roles of EVI1 in breast carcinoma. Cancer Res 2017;77:2148–60.

RNA Regulation of the DNA Damage Response



The DNA damage response (DDR) modifies chromatin to ensure repair factors can access and inhibit transcription in damaged regions. Xiang and colleagues report rapid and transient methylation at the 6th position of adenosine (m^6A) in RNA transcripts, in response to ultraviolet (UV) irradiation. This modification occurred on polyA transcripts localized to DNA damage sites, was executed by methyltransferase-like 3 and 14 (METTL3/14), and was subsequently removed by the fat mass and obesity-associated demethylase. Interestingly, methylation was also mediated by PARP, possibly recruiting METTL3 to DNA damage sites. Following UV irradiation, accumulation of m^6A was required to recruit DNA polymerase κ (Pol κ) to DNA damage sites. These data demonstrate a novel role for RNA methylation in the DDR and identify a new UV-induced DNA damage repair pathway involving METTL3, m^6A RNA, and Pol κ. *(Image courtesy of Wikimedia Commons.)*

Xiang Y, Laurent B, Hsu CH, Nachtergaele S, Lu Z, Sheng W, et al. RNA m6A methylation regulates the ultraviolet-induced DNA damage response. Nature 2017;543:573–6.

Note: Breaking Advances 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.