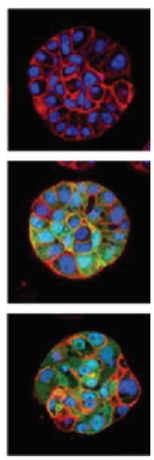
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
American Association for Cancer Research

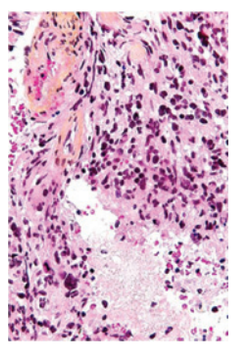
EFA6B—A Novel Antagonist of Breast Cancer



Triple-negative breast cancer (TNBC) shows low overall survival and high recurrence, and these cancers are enriched for a new claudin-low breast cancer subtype. EFA6B (Exchange Factor for ARF6 isoform B, PSD4) is a guanine nucleotide exchange factor for the Ras superfamily protein ARF6 that helps assemble tight junctions. Low levels of EFA6B were also enriched in aggressive triple-negative and claudin-low breast cancer subtypes. Zangari and colleagues observed that EFA6B was required to maintain apico-basal cell polarity. Downregulating EFA6B expression correlated with a mesenchymal phenotype, and ectopic expression inhibited TGFβ-induced epithelial–mesenchymal transition (EMT). EFA6B repression was also associated with loss of tight junction components and with increased EMT, cancer stemness, and poor prognosis in human breast tumor samples. Thus, EFA6B represents a novel therapeutic target that antagonizes early stages of breast cancer by hampering tight junction disassembly and loss of epithelial polarity. (*Image from cited article courtesy of publisher.*)

Zangari J, Partisani M, Bertucci F, Milanini J, Bidaut G, Berruyer-Pouyet C, et al. EFA6B antagonizes breast cancer. Cancer Res; Published OnlineFirst August 12, 2014; doi:10.1158/0008-5472.CAN-14-0298.

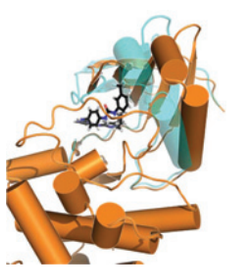
Sorting through the Genomic Rubble



Ozawa and colleagues use a mathematical model to suggest that gain of CHR7 and loss of CHR10 are early events in glioblastoma multiforme (GBM) brain tumors. Furthermore, using a computational algorithm, they identify *PDGFA* amplification and *PTEN* loss as potential drivers of the chromosomal alterations, validating in mouse models that PDGFA expression could drive murine proneural glioma. Data from paired primary and recurrent human tumors suggested that proneural tumors tend to acquire a more mesenchymal phenotype over time. In this murine model, loss of *Nf1* was sufficient to drive a mesenchymal gene signature, suggesting NF1 as a mesenchymal driver in humans. These findings suggest that GBM may initially be driven by a common set of genetic alterations and perhaps a common proneural-like precursor lesion. The optimal strategy to target these early lesions therapeutically remains to be determined. (*Image courtesy of Wikimedia Commons.*)

Ozawa T, Riester M, Cheng YK, Huse JT, Squatrito M, Helmy K, et al. Most human non-GCIMP glioblastoma subtypes evolve from a common proneural-like precursor glioma. Cancer Cell 2014;26:288–300.

MYCN Blockade by Amphisteric Inhibitors of Aurora Kinase A

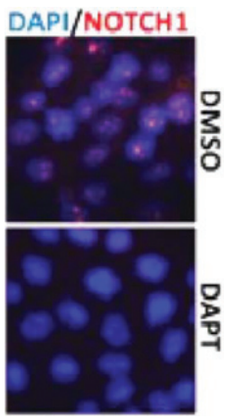


While orthosteric targeting of kinases is routine, kinases may have important nonenzymatic activities, including scaffolding of other proteins. Gustafson and colleagues synthesize and characterize an ATP-mimetic molecule (CD532) that binds and inhibits the active site of Aurora A (AURKA), altering the kinase activity of Aurora A, and inducing an amino terminal allosteric shift. This allosteric shift blocked kinase-independent stabilization of MYCN, driving degradation of MYCN in MYCN-driven neuroblastoma and medulloblastoma tumors. Whereas allosteric inhibitors bind at one site of a molecule to influence function at another site, CD532 is suggested to act "amphosterically," simultaneously at both orthosteric (inhibiting kinase activity) and allosteric sites (disrupting protein–protein interactions). CD532 thus represents a novel small molecule that induces an allosteric change to disrupt nonenzymatic functions of Aurora Kinase A. (*Image courtesy of Justin Meyerowitz, University of California, San Francisco.*)

Gustafson WC, Meyerowitz JG, Nekritz EA, Chen J, Benes CH, Charron E, et al. Drugging MYCN through an allosteric transition in Aurora Kinase A. Cancer Cell 2014 Sept 8 [Epub ahead of print].

Breaking Advances

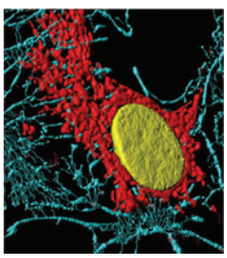
Notch-Dependent Esophageal Adenocarcinoma



The incidence of esophageal adenocarcinoma (EAC) has risen dramatically, ranking sixth in cancer mortality worldwide. Thus, a more complete understanding of molecular mechanisms driving EAC is needed to develop targeted therapies. Wang and colleagues explore roles for Notch signaling in multiple aspects of EAC carcinogenesis. They show that Notch signaling drives a significant proportion of EAC, establishing and maintaining a cancer stem cell–like population, which likely underlies therapy resistance. Using patient-derived xenograft models, the authors also demonstrate that inhibition of Notch signaling by γ-secretase inhibitors (GSI) attenuated tumor growth. Further, levels of Notch activity in patient-derived endoscopic ultrasound-derived biopsies were correlated inversely with chemotherapy response. These data suggest that inhibition of Notch activity by GSI will sensitize cells to chemotherapeutic agents, which could lead to better and more durable responses. (*Image from cited article courtesy of publisher.*)

Wang Z, Da Silva TG, Jin K, Han X, Ranganathan P, Zhu X, et al. Notch signaling drives stemness and tumorigenicity of esophageal adenocarcinoma. Cancer Res; Published OnlineFirst August 27, 2014. doi: 10.1158/0008-5472.CAN-14-2051.

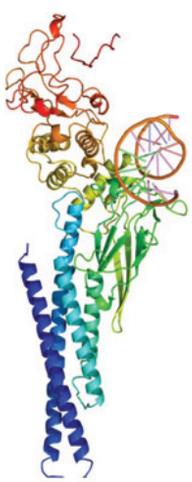
Turning on the Heat in Cancer



Scherz-Shouval and colleagues report that transcriptional regulator heat shock factor 1 (HSF1) is frequently activated in cancer-associated fibroblasts (CAF) in several human cancers as well as in the stroma of subcutaneously implanted MCF7 breast cancer cells in mice. Importantly, coinjection of carcinoma cells with fibroblasts (MEF) stimulated tumor growth *in vivo*, with *HSF1*-negative MEFs failing to similarly support progression. Coculturing of tumor cells with HSF1-expressing CAFs induced non–cell-autonomous upregulation of genes that enhanced malignant potential and downregulation of genes involved in host immune defense response. Conversely, cancer cells induced HSF1-dependent transcriptional reprogramming of the coculture fibroblasts. Among upregulated genes in the fibroblasts, TGFβ (*TGFB1*) and SDF1 (*CXCL12*) were functionally important for stroma to support tumor growth. These findings are significant therapeutically, because high stromal HSF1 was associated with poor outcome in early-stage breast cancer and lung cancer. (*Image courtesy of Wikimedia Commons.*)

Scherz-Shouval R, Santagata S, Mendillo ML, Sholl LM, Ben-Aharon I, Beck AH, et al. The reprogramming of tumor stroma by HSF1 is a potent enabler of malignancy. Cell 2014;158:564–78.

Stat3 Activation as a Broad Cell-Protective Mechanism



Mechanisms of resistance to targeted therapies are heterogeneous. Lee and colleagues set out to determine whether drug-sensitive, oncogene-addicted cells secrete factors from the tumor microenvironment that promote cell survival. Their investigations identify STAT3 activation through IL6R and FGFR as contributing to resistance by protecting cells from apoptosis in response to targeted inhibition of oncogenic kinases. Mechanistic studies reveal that inhibition of MEK is tightly linked to activation of STAT3 and serves as a cell-protective feedback mechanism that is broadly conserved across oncogene-addicted cancers that respond to kinase inhibition. These findings provide a strategy to potentially resensitize oncogene-addicted cells by disrupting the STAT3 feedback inhibition in combination with targeted inhibition in a variety of cancer cells. (*Image courtesy of Wikimedia Commons.*)

Lee HJ, Zhuang G, Cao Y, Du P, Kim HJ, Settleman J. Drug resistance via feedback activation of Stat3 in oncogene-addicted cancer cells. Cancer Cell 2014;26:207–21.

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.