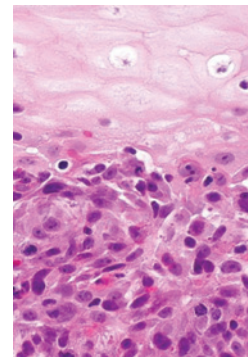


## Notch Mutations Unlevel the Playing Field

In field cancerization, fields of mutant cells replace normal cells, such that a field of apparently "normal" but in reality mutant cells may drive recurrence after therapy. Here, studying the development of esophageal premalignant lesions, Alcolea and colleagues show, using chemical carcinogenesis, lineage tracing, and mathematical models, that Notch mutant clones are unable to differentiate and therefore they continue to expand. Mutant clones foster the differentiation of normal surrounding cells that are outcompeted, a process enhanced by *TP53* mutation. Upon completion of colonization, differentiation and proliferation are rebalanced, establishing a self-maintaining large mutant population with transformation potential. The new rebalanced state may allow modeling of second primary tumor occurrence after surgery and radiotherapy. (Image courtesy of Wikimedia Commons.)

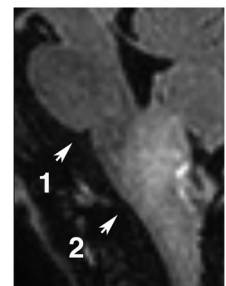
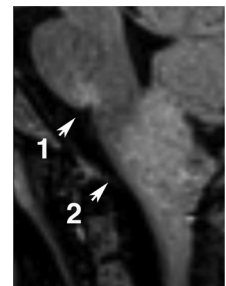
Alcolea MP, Greulich P, Wabik A, Frede J, Simons BD, Jones PH. Differentiation imbalance in single oesophageal progenitor cells causes clonal immortalization and field change. *Nat Cell Biol* 2014;16:615–22.



## Targeting Autophagy and BRAF<sup>V600E</sup> in Pediatric Glioma

Mulcahy Levy and colleagues evaluated the therapeutic implications of autophagy in pediatric gliomas driven by *BRAF*<sup>V600E</sup>. Amino acid-starved *BRAF* mutant glioma cells exhibited high rates of autophagy. The lysosomal agent chloroquine (CQ) synergized with both vemurafenib and with chemotherapy in *BRAF*<sup>V600E</sup>-positive cells, and the combination of CQ and vemurafenib was antagonistic in *BRAF* wild-type cells. In a patient with recurrent *BRAF*<sup>V600E</sup>-mutant glioma, treatment with CQ and vemurafenib led to radiographic and clinical improvement, with resumption of tumor growth after discontinuing vemurafenib. These data highlight the possibility of targeting autophagy in combination with either targeted or cytotoxic therapy as a treatment strategy in tumors primed for autophagy driven by *BRAF*<sup>V600E</sup>. (Image from cited article courtesy of publisher.)

Mulcahy Levy JM, Thompson JC, Griesinger AM, Amani V, Donson AM, Birks DK, et al. Autophagy inhibition improves chemosensitivity in BRAFV600E brain tumors. *Cancer Discovery*; Published OnlineFirst May 13, 2014; doi:10.1158/2159-8290.CD-14-0049.



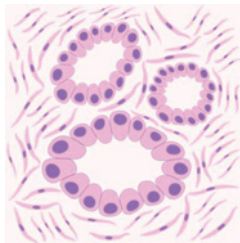
## An Emerging Oncogene Involved in MET and Integrin Stability

MET tyrosine kinase receptor signaling is frequently upregulated in almost all human cancers. The established mechanisms driving MET activation in cancer are activating mutations, receptor amplification, and increased secretion of the MET ligand, the hepatocyte growth factor (HGF). Tensin-4 (TNS4), a cytoplasmic scaffold protein that interacts with integrins, is upregulated in several cancers. While TNS4 facilitates EGFR signaling and EGF-induced migration, mechanisms underlying its oncogenic properties are largely unknown. Using a yeast-two-hybrid screen for MET receptor tyrosine kinase, Muharram and colleagues identified an unprecedented interaction between the SH2-domain of TNS4 and phospho-MET in gastric, colon, and ovarian cancers. Unexpectedly, TNS4 was essential for the stability of MET and  $\beta$ 1-integrin proteins in different cancer lines. Loss of *TNS4* reduced MET levels, inhibited MET downstream signaling, and attenuated proliferation and survival, especially in *MET*-amplified gastric carcinoma cells and *in vivo*. Mechanistically, TNS4 increased plasma membrane retention of MET and  $\beta$ 1-integrin, inhibiting their endocytosis and subsequent lysosomal degradation. Thus, TNS4 functions as an oncogene by stabilizing MET. (Image courtesy of Wikimedia Commons.)

Muharram G, Sahgal P, Korpela T, De Franceschi N, Kaukonen R, Clark K, et al. Tensin-4-dependent MET stabilization is essential for survival and proliferation in carcinoma cells. *Dev Cell* 2014;29:421–36.



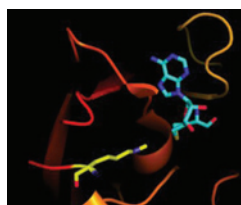
## Adding a Dose of Genomic Medicine to Cancer Treatment



The Lung Cancer Mutation Consortium evaluated the feasibility of simultaneously testing 10 oncogenes (three different assays) for driver mutations in patients with lung adenocarcinoma. Among 1,017 patients, oncogenic drivers were found in 64%, including *KRAS* (25%), *EGFR* (21%), and *ALK* (8%). Targeted therapies or clinical trials were available for 28% of these patients. The median survival was 3.5 years for *EGFR/ALK* patients, 4.9 years for patients with other drivers, and 2.5 years for patients with identified oncogenic drivers who did not receive targeted therapy. This report from Kris and colleagues underscores the necessity of performing collaborative clinical trials to identify rare patients with targetable driver mutations who are likely to benefit from novel and rational, rather than empiric, treatment approaches. (Image courtesy of Wikimedia Commons.)

Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *2014;311:1998–2006.*

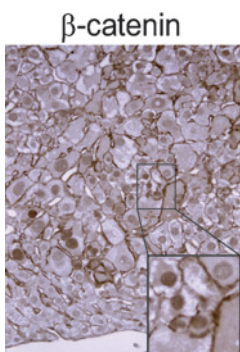
## A Lysine Methyltransferase Promotes Ras-Driven Cancers



The histone lysine methyltransferase (KMT) *SMYD3* is overexpressed in RAS-driven cancers, with loss of *SMYD3* decreasing RAS-driven carcinogenesis and increasing survival in pancreatic and lung cancer mouse models. Attenuation of carcinogenesis in these models could be reversed by expressing wild-type but not catalytically inactive *SMYD3*. *MAP3K2* was the only identified substrate of *SMYD3*, and *SMYD3* was the only KMT capable of methylating *MAP3K2*. Methylation of *MAP3K2* increased MAP kinase signaling by decreasing its affinity for the PP2A phosphatase complex. These findings from Mazur and colleagues show the potential role of direct lysine methylation of signaling proteins as an alternate way that KMTs contribute to carcinogenesis as well as the therapeutic potential of *SMYD3* inhibitors in RAS-driven cancers. (Image courtesy of Wikimedia Commons.)

Mazur PK, Reynoird N, Khatri P, Jansen PW, Wilkinson AW, Liu S, et al. *SMYD3* links lysine methylation of *MAP3K2* to Ras-driven cancer. *Nature* 2014 May 21 [Epub ahead of print].

## HCC in Liver Progenitor Cells Following $\beta$ -Catenin Activation



Mokkapati and colleagues identify a unique population of fetal liver progenitor cells in mice that can initiate hepatocellular carcinoma (HCC). Because the Wnt pathway (activated in 50% of HCC) regulates stem/progenitor cell self-renewal, the authors hypothesized that Wnt activation in fetal liver progenitor cells might initiate HCC. Over 90% of transgenic mice that expressed a *Ctnnb1* conditionally stabilized allele under control of *Cited1*, a transcriptional coactivator protein for CBP/p300, developed HCC, and in some cases, developed hepatoblastomas and lung metastases. Thus, Wnt pathway activation alone was able to transform the unique liver progenitor cells identified and supports the finding that HCC can be initiated in fetal/adult progenitor cells. This novel model provides insight into the etiology of HCC and hepatoblastomas and enables development of novel therapeutics. (Image from cited article courtesy of publisher.)

Mokkapati S, Niopek K, Huang L, Cunniff KJ, Ruteshouser EC, deCaestecker M, et al.  $\beta$ -catenin activation in a novel liver progenitor cell type is sufficient to cause hepatocellular carcinoma and hepatoblastoma. *Cancer Res*; Published OnlineFirst May 21, 2014; doi:10.1158/0008-5472.CAN-13-3275.

**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.