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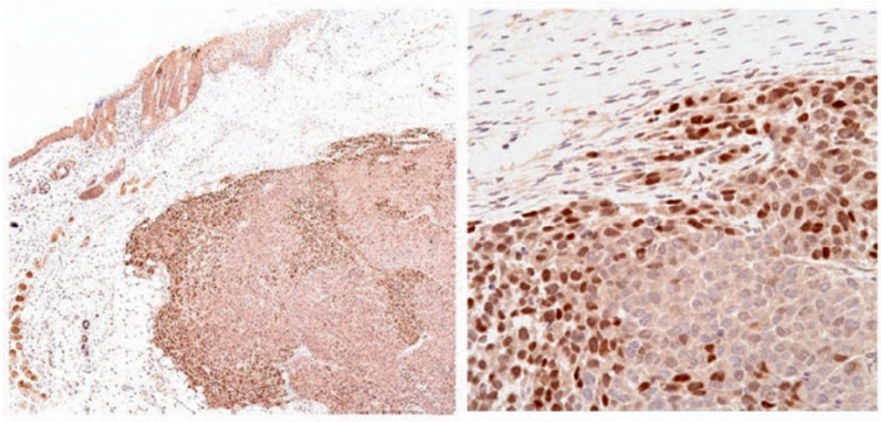


SOX2 contributes to melanoma cell invasion

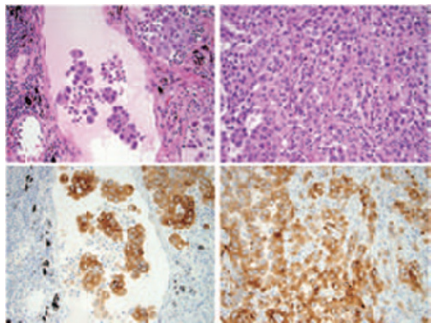
See page 362

Melanoma cell invasion is associated with a poor prognosis. Therefore, determining its mechanisms could yield therapeutic strategies to impair invasion and dissemination. One potential strategy to identify determinants of melanoma cell invasion is to identify genes involved in progenitor cell migration that are abnormally expressed in melanoma. SOX2 is an important transcription factor involved in embryonic stem cell pluripotency and in maintenance of physiologically migratory neural progenitor cells. There is some evidence that SOX2 contributes to the malignant phenotype in a variety of poorly differentiated cancers. Recently, SOX2 was found to be expressed in 14% of nevi, 67% of primary melanomas, and 80% of metastatic melanomas. Furthermore, 3-year median survival was significantly lower in patients with melanoma that expressed SOX2. Based on these data, Girouard *et al* hypothesized that SOX2 may be involved in melanoma invasion.

By examining melanoma tissue sections the authors found that SOX2 was preferentially expressed in cells located at the interface of invasion. Knockdown of *SOX2* in melanoma cells that had high-level *SOX2* expression resulted in impairment of invasion *in vitro*. Conversely, overexpression in melanoma cells that expressed *SOX2* poorly enhanced invasion *in vitro*. Examination of genes encoding proteins that might play a role in invasion demonstrated that SOX2 controlled expression of matrix metalloproteinase 3 (MMP3). Indeed, SOX2 and MMP3 were often coexpressed in melanoma cells in areas of melanoma cell invasion. These results suggest that SOX2 is important in controlling melanoma cell invasion and that at least part of the invasive phenotype is determined by MMP3 expression.

Overcoming therapeutic resistance in EGFR-driven lung cancer

See page 371



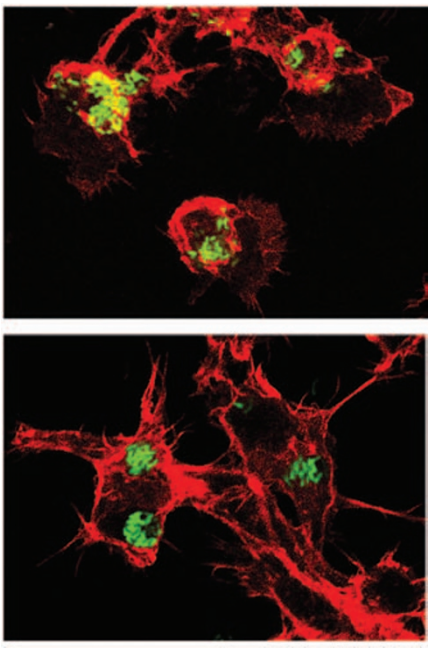
Epidermal growth factor receptor (EGFR) is a member of the HER/ErbB family of receptor tyrosine kinases. Activating mutations in EGFR can deregulate downstream signaling activity, leading to cancer. Approximately 10–15% of all non–small cell lung carcinomas (NSCLCs) in Caucasians, 20–30% of all NSCLCs in East Asians, and up to 50% of NSCLCs in patients who have never smoked have *EGFR* mutations. Because these oncogenic EGFR proteins drive ligand-independent constitutive activation in these NSCLCs, they are addicted to mutant EGFR. EGFR-driven NSCLCs have become a paradigm for "oncogene addiction." The important consequence of oncogene addiction to EGFR is that EGFR has become an important therapeutic target in NSCLCs that harbor *EGFR* mutations. Two oral tyrosine kinase inhibitors (TKIs) that target EGFR have considerable efficacy in EGFR-driven NSCLC. However, many patients develop resistance and tumor progression. This has led to several therapeutic strategies that leverage the effectiveness of EGFR TKIs to fully eradicate the tumor cells. In this issue, Sakuma *et al* describe one of these strategies.

Their report has two important messages. One is that tumor emboli, or nonadherent tumor cells, are more sensitive to TKIs than adherent cells are. The second is that the combination of a novel, third-generation EGFR TKI, WZ4002; an Src inhibitor; and a histone deacetylase inhibitor has the potential to eradicate EGFR-driven lung cancers, even when the cells are resistant to conventional EFGR TKIs. This is presumably due to the greater potency of WZ4002 and the combination of other drugs that target Src activation and the epigenetic landscape.

TNF-α secretion has unintended consequences in Crohn's disease

See page 411

Crohn's disease is a relatively common form of idiopathic inflammatory bowel disease. Current theories regarding the pathogenesis of Crohn's disease suggest that genetic immunologic deficiencies result in the inability to deal with gastrointestinal-based pathogenic bacteria. The *NOD2* (nucleotide-binding oligomerization domain 2) gene and the autophagy genes *ATG16L1* and *IRGM* are genetic susceptibility loci that encode proteins involved in the recognition and elimination of intracellular bacteria. Adherent-invasive *Escherichia coli* (AIEC) lie at the heart of Crohn's disease pathogenesis,



and the inability of macrophages to eliminate AIEC correlates with the disorder. This commonly occurs through pathogen-induced macrophage apoptosis. However, AIEC-infected macrophages do not undergo apoptosis, suggesting that AIEC is able to actively inhibit macrophage apoptosis. AIEC macrophages secrete large amounts of tumor necrosis factor-α (TNF-α), implicating TNF-α in the inhibition of macrophage apoptosis.

Bringer *et al* sought to understand the relationship between macrophage TNF-α secretion and AIEC as a potential Achilles' heel that could be exploited in the treatment of Crohn's disease. They found that TNF-α secretion was dependent both on extracellular pattern-recognition receptor stimulation and on intramacrophagic AIEC bacteria stimulation. Furthermore, TNF-α stimulated AIEC replication. Thus, AIEC set up a positive feedback loop in which the more they replicate, the more macrophage TNF-α takes place, which in turn increases AIEC replication. The authors speculate that the mechanism of TNF-α stimulation of AIEC replication relates to inhibition of macrophage apoptosis or enhanced phagosome maturation. Their results clearly suggest that inhibition of AIEC replication is a useful therapeutic strategy in Crohn's disease.

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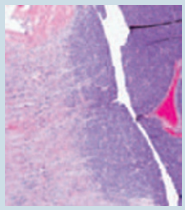
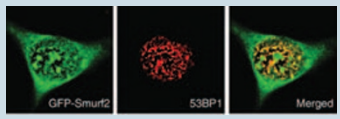
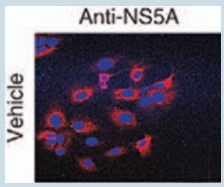


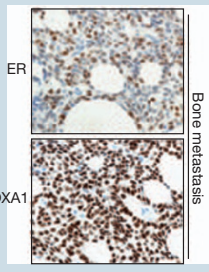
SYK is a novel target in retinoblastoma Retinoblastoma is a rare childhood cancer of the retina that arises from bi-allelic inactivation of *RB1*. Previous studies have shown that the functional inactivation of RB1 can lead to genetic instability. Therefore, as described in a recent article in *Nature*, Zhang *et al* were surprised to find that retinoblastoma is stable genetically. Using whole-genome sequencing, they failed to identify any additional driver mutations. By integrating whole-genome sequencing with chromatin immunoprecipitation data, DNA methylation, and gene expression assays, they found 104 genes, including 15 known cancer genes that were epigenetically regulated. They focused on SYK (spleen tyrosine kinase) because it is a kinase and there are SYK inhibitors in clinical trials. Treatment with SYK inhibitors suggested that SYK is a promising new target for treating retinoblastoma.
Nature 2012;481:329–334; doi:10.1038/nature10733



Smurf2 is a tumor suppressor Smad ubiquitin regulatory factor 2 (Smurf2), an E3 ubiquitin ligase, has several recognized substrates, and there is evidence suggesting a role for Smurf 2 in tumorigenesis. In an attempt to define the physiological role of Smurf2, Blank *et al*, as recently reported in *Nature Medicine*, ablated Smurf 2 in a mouse model. They discovered that *Smurf2*$^{-/-}$ mice developed a diverse repertoire of cancers late in their life span. Mechanistic evaluation indicated that there was a defect in DNA damage response and genomic instability in *Smurf2*$^{-/-}$ mouse embryonic fibroblasts. The authors were able to link loss of Smurf2 to genomic instability by demonstrating that ring-finger protein 20 (RNF20) is a substrate of Smurf2. RNF20 is the major E3 ligase responsible for monoubiquitin modification of histone H2B (ubH2B). Thus, loss of Smurf2 results in elevated ubH2B, which dramatically alters the epigenome. These results provide additional evidence that epigenomic alterations can lead to cancer.
Nature Medicine, published online 8 January 2012; doi:10.1038/nm.2596



New hepatitis entry vector identified Hepatitis C virus (HCV) is thought to enter hepatocytes through interaction with a variety of cellular entry factors. It is known that HCV is enriched in cholesterol, which is necessary for HCV hepatocyte entry. This led Sainz *et al*, as described in a recent letter in *Nature Medicine*, to hypothesize that cholesterol-uptake receptors might play a role in HCV cell entry. They found that Niemann–Pick C1–like 1 cholesterol absorption receptor (NPC1L1) was required for HCV cell entry and that entry was dependent on the presence of cholesterol. Ezetimibe, a cholesterol-lowering medication approved by the US Food and Drug Administration, is a direct inhibitor of NPC1L1 internalization. Its use resulted in decreased infection of HCV *in vitro* and *in vivo*. NPC1L1 is therefore a target for prevention of HCV infection.
Nature Medicine, published online 8 January 2012; doi:10.1038/nm.2581



Prognostic importance of differential ER binding in breast cancer Estrogen receptor (ER) binding is a key oncogenic event in most breast cancers. However, much of what is known about ER binding has been learned from model systems that may not adequately represent breast cancer *in vivo*. In a recent letter in *Nature*, Ross-Innes *et al* report their investigation of ER binding in actual primary and metastatic breast cancer samples using chromatin immunoprecipitation followed by high-throughput sequencing. They discovered that the pattern of ER binding was different in drug-resistant versus sensitive breast cancers, resulting in a pattern of gene expression that correlated with prognosis. Interestingly, their analysis revealed that ER-binding differences were preceded by FOXA1 binding, suggesting that FOXA1 is able to reprogram ER binding.
Nature, published online 4 January 2012; doi:10.1038/nature10730