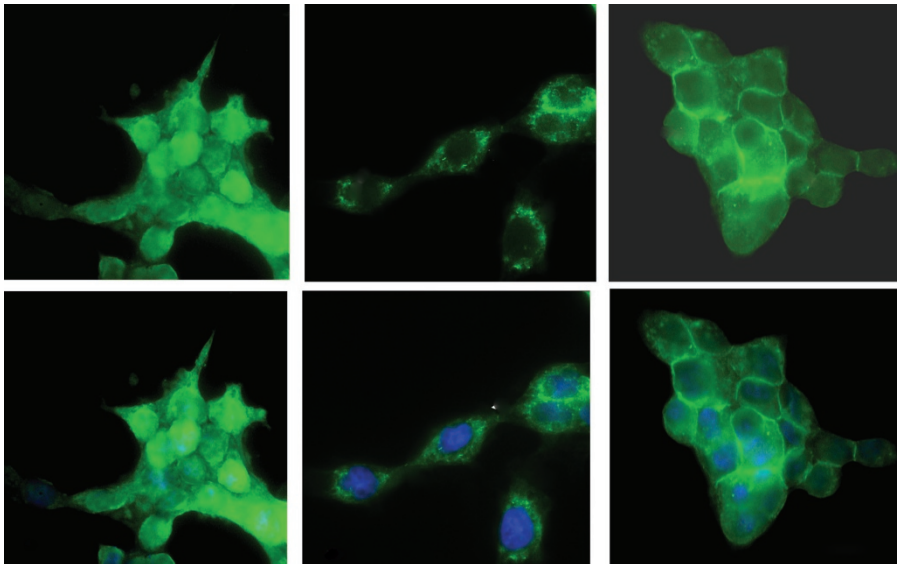
Laboratory Investigation (2009) 89, 486-487

INSIDE LAB INVEST

doi:10.1038/labinvest.2009.31



Versatile player in colon cancer

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Colorectal cancer is the third most common cancer diagnosed in both men and women in the United States, with about 150,000 new cases and 50,000 deaths in 2008. Although considerable progress has been made in the treatment of colorectal carcinoma, there is more room for improvement. Neutrophil gelatinase–associated lipocalin (NGAL)/lipocalin2 is overexpressed in a variety of common cancers and is thus thought to play a role in their pathophysiology. However, not much is known about the role of NGAL with respect to solid tumors.

Hu *et al* sought to understand the role of NGAL in colon cancer. Interestingly, they found that NGAL exerts its effects through several mechanisms. By developing a series of isogenic cell lines that differ in the amount of NGAL that is expressed, they showed that overexpression of NGAL was associated with more aggressive behavior, such as increased cell motility and *in vitro* invasion. The effect is reversed when NGAL is underexpressed. The effects on motility appear to be mediated by sequestration of E-cadherin from cell–cell junctions in a Rac1-dependent manner. Also of interest, NGAL has been reported to be an iron-transport protein. NGAL conferred an increased ability to tolerate high iron concentrations, and iron levels were found to play an important role in NGAL-dependent Rac1 distribution. This initial report is certain to provoke further studies on the role of NGAL in colon cancer and places NGAL on the growing list of potential therapeutic targets for this important cancer.

Micro-RNA from archival tissues

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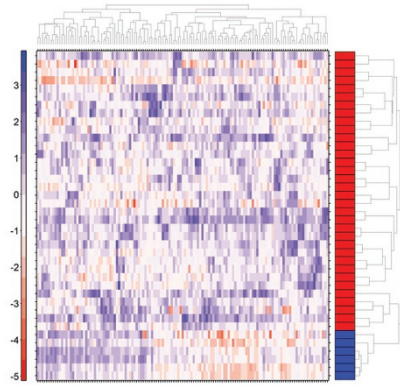
Micro-RNAs (miRs)—very small RNAs approximately 22 nucleotides in length—regulate protein expression by binding to complementary regions of mRNAs that target them for destruction. There are approximately 450–1000 miRs in the human genome, and each miR is thought to target as many as 200 distinct mRNAs. Thus, miRs have the potential to regulate virtually every cellular function. Global miR profiling has been performed on various cancers. miR profiles can distinguish one type of cancer from another, predict clinical outcome, and identify proteins that are important in the pathogenesis of cancer. Most miR profiling has been performed using frozen tissues.

To broaden the applicability of miR, Hui and colleagues performed a rigorous evaluation of miR profiling using miR derived from formalin-fixed paraffin-embedded (FFPE) tissues. They compared 34 invasive ductal carcinomas of the breast with six normal breast samples. Using a quantitative real-time polymerase chain reaction–based platform, they found that the technique was highly reproducible, achieved results comparable to those of paired frozen samples, was validated by an alternative approach, and produced biologically meaningful information. This



is good news for pathologists because it means that archival samples can be used for miR profiling and analysis, opening the door for the study of our vast archives of well-validated FFPE tissues.

Tumor microenvironment and metastasis

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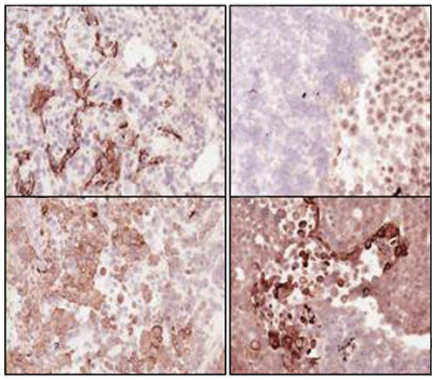
The tumor microenvironment is known to play critical roles in tumor maintenance and tumor cell behavior.

While many factors are involved in the tumor microenvironment, there has been particular interest in the influence of hypoxia. Hypoxic conditions, which exist in virtually all rapidly growing tumors, require considerable adaptation to deal with the lack of molecular oxygen available to tumor cells.



Chaudary and Hill have hit on an interesting technique for probing hypoxic tumor cells in order to study how they cope with limited oxygen. Using an orthotopic cervical cancer model that is capable of metastasis, they used sophisticated fluorescence-activated cell-sorting analysis with a tumor-specific marker and carbonic anhydrase-9, a marker of hypoxia. This technique facilitates purification of hypoxic tumor cells for further study. In the current study, they found that several metastasis-related proteins, including CXCR4, uPAR, VEGFC, Hdm2, and OPN, were expressed in hypoxic cells from both primary tumors and metastasis. One of the interesting twists in this study is that these genes were not elevated during chronic hypoxia but were elevated during acute hypoxia. In aggregate, these results suggest that hypoxia may play a role in initiating metastasis. If this turns out to be the case, then understanding which genes are involved in this process could lead to therapies aimed at inhibiting metastasis.

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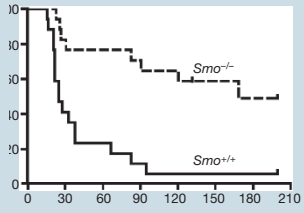
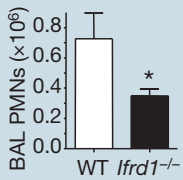
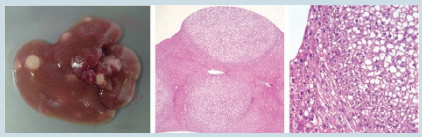


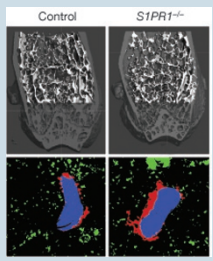
Achilles heel in cancer stem cells In recent years, significant progress has been made in understanding the role of cancer stem cells. In a recent letter in *Nature*, Zhao *et al* examine the role of Hedgehog (Hh) signaling in cancer stem cells in chronic myelogenous leukemia (CML). By manipulating Smoothened (Smo), which is essential for Hh signaling, either by conditional deletion or by the expression of constitutively activated Smo, they decreased or increased the stem cell compartment in a mouse model of BCR-ABL1-induced CML. Pharmacologic inhibition of Smo by cyclopamine also resulted in decreased tumor growth and increased survival. These results are particularly important in CML, in which imatinib mesylate is an effective treatment but cannot eradicate the cancer stem cell compartment, necessitating lifelong treatment. The results suggest that the combination of imatinib with ablation of the Hh pathway by small-molecule inhibitors may act synergistically in the treatment of CML.
Nature, published online 25 January 2009; doi:10.1038/nature07737



New gene involved in cystic fibrosis lung disease The identification of *CFTR* mutations and subsequent discovery of the role of *CFTR* in regulating epithelial iron transport was a landmark in the study of cystic fibrosis (CF). However, the link between *CFTR* mutations and the manifestations of lung disease in CF has been elusive. In a recent letter in *Nature*, Gu and colleagues describe their use of genome-wide association analysis to identify genetic modifiers of lung disease in CF patients. They identified IFRD1, a histone-deacetylase-dependent transcriptional coregulator expressed during neutrophil differentiation. Elegant experiments in a mouse Ifrd1 knockout model showed that Ifrd1 is necessary for neutrophil function in an NF-κB-dependent manner. Since neutrophil dysfunction is a hallmark of CF, the identification of IFRD1 polymorphisms provides a plausible link between disease manifestations and protein function. These results highlight IFRD1 as a potential target for CF therapy.
Nature, published online 25 February 2009; doi:10.1038/nature07811



Powerful genetic system for mouse models Transposon-based mutagenesis using the *Sleeping Beauty* (*SB*) system has been developed recently for use in mouse models. However, the utility of this system has been hampered by the development of fatal lymphomas at an early age. That limitation has now been overcome. In a recent letter in *Nature Biotechnology*, Keng *et al* introduce a modification of the system that enables lineage-restricted expression of the SB transposase through Cre recombinase. The system was validated using a liver-specific albumin-Cre driver that led to a spectrum of liver tumors from adenomas to metastatic hepatocellular carcinomas (HCCs), which were further characterized to identify transposon insertion sites. These data were compared with genomic data from human HCCs to highlight potential therapeutic targets in HCC. The design of this system should be a boon to cancer research because it can be used with a wide variety of lineage-specific Cre drivers.
Nature Biotechnology 2009;27:264–274; doi:10.1038/nbt.1526



Regulation of osteoclast precursor movement Regulation of osteoclasts by competing pathways that attract osteoclast precursors to and from the bone surface has important implications for normal and pathologic conditions. In a recent letter in *Nature*, Ishii and coworkers identify sphingosine-1-phosphate (S1P) as a regulator of osteoclast-precursor mobilization. S1P stimulates movement of osteoclast precursors, resulting in loss of osteoclasts from the bone surface. S1P receptor agonists inhibit bone-density loss in ovarectomized mice by stimulating osteoclast precursors to mobilize from the bone surface. Conversely, S1P knockout mice are osteoporotic in comparison with littermate controls. These results identify S1P as a pharmacologic target for diseases involving bone homeostasis.
Nature, published online 8 February 2009; doi:10.1038/nature07713