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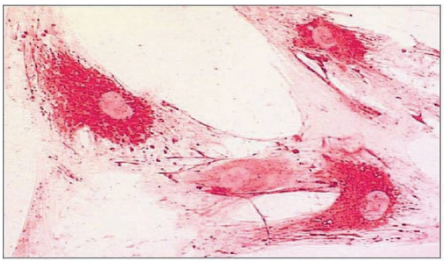

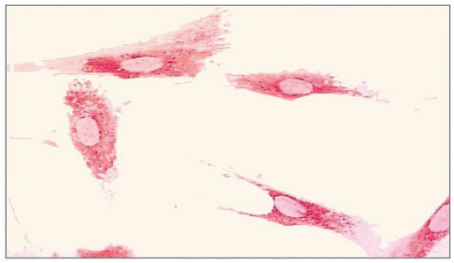

Loss of Thy-1 promotes profibrotic phenotype in IPF

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Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive form of often fatal lung disease characterized by a set of histological features known as usual interstitial pneumonia. There is extensive collagen deposition/fibrosis within the pulmonary interstitium with minimal inflammation. The etiology of IPF remains obscure, and there is no satisfactory treatment. To investigate the pathogenesis of IPF, researchers have focused their attention on pulmonary fibroblasts. Fibroblasts transdifferentiate into myofibroblasts, forming characteristic fibroblast foci. One recent important observation is that the fibroblasts in fibroblast foci are Thy-1 negative whereas fibroblasts in the normal lung are Thy-1 positive. Thy-1, or CD90, is a cell-surface glycophosphatidylinositol-linked glycoprotein that activates signaling pathways and participates in various cellular functions. To determine how loss of Thy-1 contributes to fibrogenesis in IPF, Ramírez *et al* developed a Thy-1 negative fibroblast cell line from an IPF patient.

The authors found that transforming growth factor-β1 (TGF-β1) induced expression of matrix metalloproteinase-9 (MMP-9) in Thy-1-negative fibroblasts but not in Thy-1-positive fibroblasts. Production of MMP-9 was dependent on ERK1/2 signaling. Furthermore, Thy-1 fibroblasts in fibroblastic foci were strongly immunoreactive for MMP-9 *in vivo*, validating the *in vitro* findings and suggesting that MMP-9 plays an important role in the pathogenesis of IPF. MMP-9 is associated with the degradation of collagen IV, a main component of basement membrane, but it also proteolytically cleaves TGF-β, suggesting that TGF-β induction of MMP-9 in Thy-1 negative fibroblasts could result in a positive fibrogenic feedback loop. Overall, these results suggest that controlling production of MMP-9 by fibroblasts in IPF could be a key to successful IPF therapy.

Inhibition of autophagy sensitizes cholangiocarcinoma cells to chemotherapy

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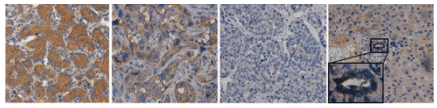

Cholangiocarcinoma, a malignant neoplasm that arises from intrahepatic bile ducts, has a dismal prognosis. Although it is rare, its incidence has been increasing steadily. The mainstay of therapy is surgery. Unfortunately, most patients present at a late stage and are thus unresectable. Because cholangiocarcinoma is resistant to chemotherapy, new approaches to therapy are needed.

Autophagy ("self-eating") is a primitive cellular process conserved from mammals to yeast that buffers cells against cellular stresses such as nutrient deprivation. Activation of autophagy results in the sequestration of organelles such as mitochondria into membrane-bound structures known as autophagosomes. Sequestration and degradation of organelles can contain cellular organelle damage before it activates apoptosis; they can also provide energy in energy-depleted states such as when nutrients or oxygen are low. Too much autophagy can result in cells literally digesting themselves to death. It has recently been shown that autophagy is activated in cancer cells in response to chemotherapy, facilitating cancer cell survival. In some cases, inhibition of autophagy sensitizes cancer cells to chemotherapy. Because cholangiocarcinoma cells are so resistant to chemotherapy, Hou *et al* asked whether autophagy might protect cholangiocarcinoma cells from chemotherapy.

Using cell-line models of cholangiocarcinoma, the investigators found that autophagy was activated in low-nutrient conditions and in clinical samples. They showed that inhibition of autophagy by chemical inhibitors or depletion of autophagy genes increased apoptosis in combination with nutrient deprivation or chemotherapy with cisplatin. These results suggest that combination therapy with autophagy inhibitors might sensitize cholangiocarcinoma cells to cisplatin therapy, thereby improving its efficacy.

Mechanistic insights into the efficacy of hydrogen sulfide therapy in psoriasis

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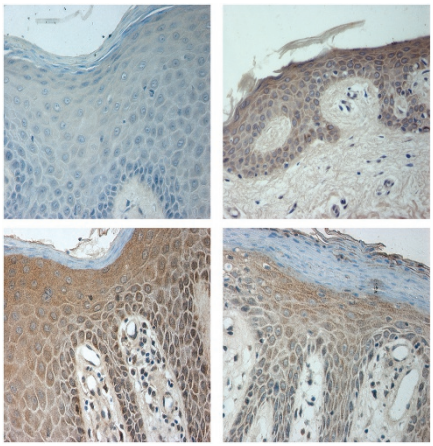
Psoriasis is an epidermal disorder with a chronic immune etiology that is characterized by proliferation of keratinocytes. Considerable evidence points to the production of interleukin-17 (IL-17) and IL-22 by T helper type 17 (Th17) immune cells as playing an important role in the pathogenesis of psoriasis. IL-17 and IL-22 induce keratinocytes to produce

IL-8, which serves as a chemoattractant for neutrophils and T lymphocytes. Induction of IL-8 production by IL-17 has been shown to be dependent on mitogen-activated protein kinase (MAPK) signaling. Recently, hydrogen sulfide therapy, which is known to be effective in the treatment of psoriasis, has been shown to inhibit the Raf-MEK-ERK/MAPK pathway. On the basis of these results, Mirandola *et al* wondered whether hydrogen sulfide therapy might inhibit IL-8 production by keratinocytes through decreased MAPK signaling.



The authors demonstrated that both IL-17 and IL-22 activated the MAPK pathway in immortalized keratinocytes. Inhibition of MAPK by U0126, a MEK inhibitor, decreased IL-8 production. Hydrogen sulfide was able to decrease MAPK signaling in keratinocytes *in vitro,* which in turn decreased the secretion of IL-8. Examination of psoriatic lesions from a patient demonstrated diffuse immunostaining for IL-8 that was diminished after hydrogen sulfide treatment. In summary, these results demonstrate that hydrogen sulfide therapy acts in part to suppress MAPK signaling in psoriatic lesions, which results in decreased IL-8 production and, presumably, decreased inflammation. Since the *in vivo* studies were done in a single patient, larger studies to examine the effects in a larger number of patients are indicated.

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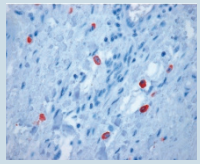
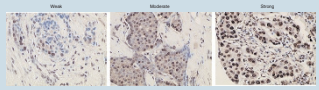
GIST prognosis correlates with immune system function



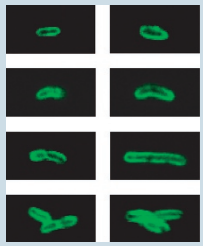
Gastrointestinal stromal tumors (GISTs), which are characterized by constitutively activating mutations in *KIT*, are treated by KIT inhibitors such as imatinib mesylate. Although most patients respond initially to imatinib, approximately 50% of those initial responders develop resistance, most commonly due to intra-allelic second-site *KIT* mutations that render KIT insensitive to imatinib. In many GIST patients, however, the mechanism of resistance is unexplained. In a recent article in *Nature Medicine,* Delahaye *et al* determined that GIST patients with the natural killer (NK) cell receptor NKp30 isoform c (NKp30c) had a worse prognosis than isoforms a and b. The poorer prognosis was attributed to an immunosuppressive phenotype of NKp30c. Interestingly, two single-nucleotide polymorphisms (SNPs) were associated with the preferential expression of NKp30c. These results suggest that genetically controlled immunosuppression by NKp30c contributes to the response to imatinib and that NKp30c SNP or functional biomarker analysis might be useful in stratifying patients for therapy.
Nature Medicine 2011;700–707; doi:10.1038/nm.2366

LMTK3 is a new therapeutic target in breast cancer

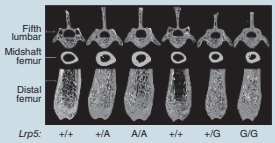


Therapies targeting estrogen receptor-α (ERα) activation such as tamoxifen, an antiestrogen, have considerable efficacy in ERα$^+$ breast cancer. However, resistance is common. Giamas *et al*, reporting in a recent letter in *Nature Medicine,* demonstrated that lemur tyrosine kinase 3 (LMTK3) increased transcription of *ERα* and stabilized the ERα protein via direct phosphorylation. Knockdown of *ERα* decreased tumor volume in an orthotopic mouse model. Furthermore, LMTK3 protein abundance and the presence of intronic polymorphisms were predictive biomarkers for disease-free and overall survival and response to antiestrogen therapies in human breast cancers. These results suggest that targeting LMTK3 might enhance the efficacy of antiestrogen therapies because LMTK3 increases ERα levels.
Nature Medicine 2011;17:715–719; doi:10.1038/nm.2351

PGRPs kill bacteria by activating a suicide program In a recent article in *Nature Medicine,* Kashyap *et al* describe the mechanism of bacterial killing by peptidoglycan recognition proteins (PGRPs)—proteins that are conserved from insects to mammals that function in antibacterial immunity by binding bacterial peptidoglycan. The authors demonstrated that PGRPs activate bacterial stress-response systems that are responsible for responding to misfolded proteins. Activation of this stress-response system results in production of hydroxyl radicals and membrane depolarization, which causes cessation of all major biosynthetic reactions. The authors speculate that overloading this system activates a suicide program that protects the bacterial population by killing bacteria that are too damaged to survive. These sensing systems could be targeted therapeutically by inexpensive peptides that could be active against multidrug-resistant bacteria.



Nature Medicine 2011;17:676–683; doi:10.1038/nm.2357



Lrp5 is an important regulator of bone mass Maintenance of bone mass is important to the health of the elderly, especially women with osteoporosis. Loss-of-function mutations in *LRP5* encoding low-density lipoprotein receptor–related protein 5 (LRP5) result in low bone mass whereas *LRP5* missense mutations lead to increased bone mass in humans. To determine the mechanism behind regulation of bone mass by Lrp5, Cui *et al*, as described in a recent article in *Nature Medicine,* engineered loss-of-function and gain-of-function *Lrp* alleles into genetically engineered mice. Osteocyte-specific expression of inactivating Lrp alleles resulted in loss of bone mass whereas gain-of-function Lrp alleles increased bone mass. These results suggest that therapies that increase LRP5 production, or that even supply exogenous LRP5, could be used therapeutically to increase bone mass in humans.
Nature Medicine 2011;17:684–691; doi:10.1038/nm.2388