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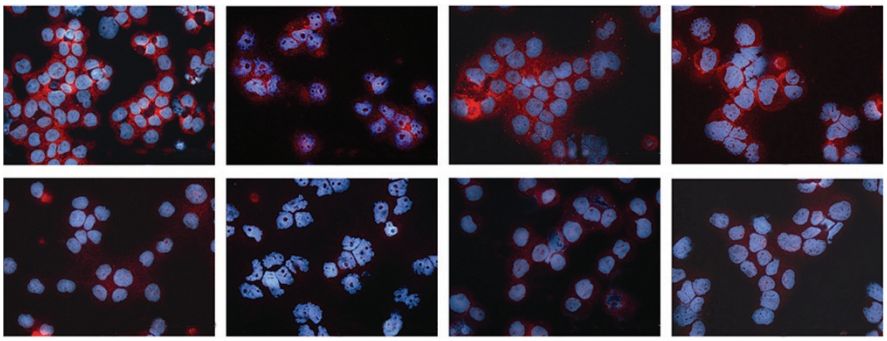

Anti-VEGF therapy targets cancer cells as well as microenvironment

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Bevacizumab (Avastin; Genentech/Roche) is a humanized monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A). Because multiple myeloma (MM), a plasma cell neoplasm, is associated with increased microvessel density in the bone marrow, clinical MM trials with bevacizumab have been initiated. However, it is possible that MM, which is known to possess VEGFR1 receptors, could be directly affected by bevacizumab in addition to any effects on microvasculature within the tumor microenvironment. To explore this possibility, Attar-Schneider *et al* treated MM cell lines in culture with bevacizumab.

The authors demonstrated that bevacizumab potently inhibited MM cell proliferation, resulting in G1 cell cycle arrest, but did not increase apoptotic or other types of cell death. Examination of intracellular signaling proteins revealed that bevacizumab decreased activation of mammalian target of rapamycin (mTOR), suggesting that autophagy might be activated. Indeed, microtubule-associated light chain II formation increased after bevacizumab treatment, indicating that autophagy was activated. Importantly, autophagy inhibition by pharmacological inhibition in combination with bevacizumab increased MM apoptosis, suggesting that autophagy was protecting bevacizumab-treated MM from cell death. Furthermore, protein translation was inhibited after treatment with bevacizumab, as demonstrated by decreased eukaryotic translation initiation factor 4E and mTOR activity. Because MM causes end-organ damage through secretion of large quantities of monoclonal immunoglobulins, decreased protein translation could also be beneficial therapeutically. Overall, Attar-Schneider *et al* demonstrated the surprising finding that there are microenvironment-independent effects of bevacizumab that directly target MM cells, suggesting that this VEGF-A inhibitor has the potential to exert therapeutic activity beyond its intended target of the tumor microvasculature.

ERp29 induces cancer cell growth arrest and survival

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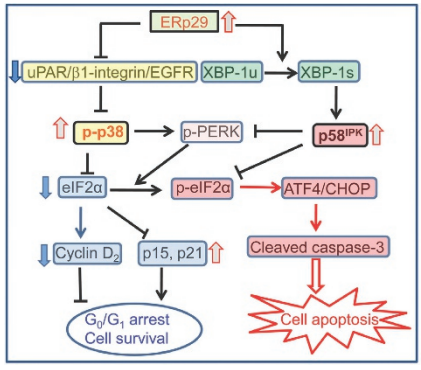

The endoplasmic reticulum (ER) is increasingly recognized as having an important role in cancer formation and response to therapy. ER protein 29 (ERp29) is an ER luminal protein with known roles in protein unfolding and secretion. It was recently reported that overexpression of ERp29 inhibited cell proliferation and tumorigenesis in a breast cancer cell line. However, the mechanism of ERp29's action is unclear. Because it is important to understand mechanisms that cancer cells use to promote survival, Gao and colleagues sought to determine how ERp29 overexpression promotes growth arrest and cell survival in breast cancer. They found that overexpression of ERp29 led to robust activation of Cdc42/p38, which directly inhibits cell cycle progression. Treatment with a specific p38 inhibitor, SB203580, reversed the cell cycle inhibitory program. Survival appeared to be mediated through inhibitor of the interferon-induced, double-stranded RNA-activated protein kinase $p58^{IPK}$, which can directly inhibit ER stress and the unfolded protein response (UPR). Depletion of $p58^{IPK}$ led to activation of the UPR in breast cancer cells that overexpresssed ERp29. Furthermore, depletion of $p58^{IPK}$ in these cells, as well as in normal breast epithelial cells that overexpressed ERp29, sensitized the cells to apoptotic cell death after treatment with doxorubicin. Thus, ERp29 overexpression may serve as a biomarker for treatment resistance in breast cancer through protection from apoptosis. These results also suggest that inhibition of ERp29 would be useful to sensitize ERp29-overexpressing cancer cells to anticancer therapies.

A novel murine model for non-alcoholic steatohepatitis

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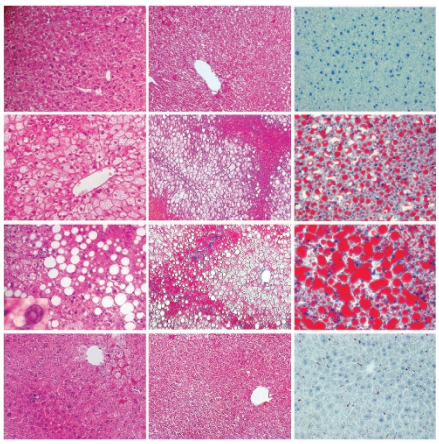
Non-alcoholic fatty liver disease (NAFLD) is associated with metabolic syndrome, a disease that has reached epidemic proportions in the United States due to high-fat diets. Non-alcoholic steatohepatitis (NASH) is an important form of NAFLD that is characterized by

liver steatosis, necrosis, inflammation, and fibrosis. NASH has the potential to progress to full-blown cirrhosis and hepatocellular carcinoma. NASH has become an enormous health problem, but there is no animal model that faithfully recapitulates the natural etiology and pathology of the disease in humans.



In a proposed two-hit hypothesis for NASH, the first hit is hepatic steatosis induced by lipid accumulation; subsequent hits contribute to the progression to steatohepatitis. Recent evidence suggests that oxidized lipids contribute to the second hits that lead to NASH. Yimin *et al* proposed that chronic administration of a high-fat diet to mice followed by intravenous administration of oxidized LDL (oxLDL), which serves as an extracellular source of reactive oxygen species, would serve as a faithful mouse model of NASH. Indeed, they found that these mice developed all the histological features of NASH seen in humans as well as the physiological findings of induced insulin resistance, hyperglycemia, and hyperinsulinemia, suggesting that oxLDL is sufficient to provide the environment for the second hits required for the development of NASH. Mechanistic evaluation of these mice pointed to a new role for CD36, expressed on hepatic macrophages and hepatocytes, as being critical for the pathogenesis of NASH by facilitating fatty-acid uptake.

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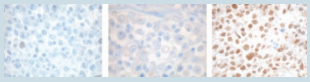
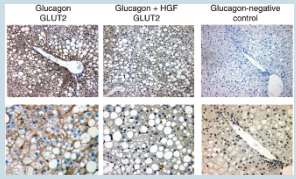
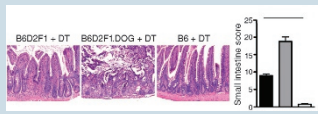


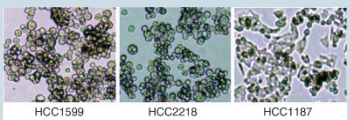
***FBXO11* mutations in diffuse large B-cell lymphomas** BCL6 is overexpressed in the majority of diffuse large B-cell lymphomas (DLBCLs). Because the degradation of BCL6 has been reported to be phosphorylation–dependent, Duan *et al* hypothesized, as described in a recent letter in *Nature,* that BCL6 is degraded by a SKP1-CUL1-F-box protein (SCF) ubiquitin ligase complex, given that most SCF ligases target phosphorylated substrates. They discovered that BCL6 was degraded by an SCF ubiquitin ligase complex containing the F-box protein FBXO11, which specifically binds to BCL6. Further analysis of DLBCL patient samples, cell lines, and databases revealed that *FBXO11* mutations were present in a small subset of DLBCLs. Because the mutations were typically monoallelic, the authors propose that FBXO11 is the product of a haplo-insufficient tumor-suppressor gene.
Nature, published online 23 November 2011; doi:10.1038/nature10688



Cooperative regulation of hepatocyte glucose metabolism by MET and insulin receptor Insulin receptor (INSR) and Met (also known as hepatocyte growth factor receptor), which are expressed by hepatocytes, contain considerable homology in their kinase regulatory loops. Notably, phosphorylation of three homologous tyrosine residues are required for maximum upregulation of catalytic activity. On the basis of these parallels between Met and INSR, Fafalios *et al* hypothesized that Met and INSR might have overlapping functions in hepatocytes, including controlling glucose metabolism. As reported in *Nature Medicine*, they demonstrated that Met and INSR form a complex that is initiated by both hepatocyte growth factor (HGF) and insulin to maximally stimulate glucose metabolism. They also showed that Met activation restored insulin response in a mouse model of type 2 diabetes, suggesting that HGF might have a therapeutic role in treating that disorder.
Nature Medicine 2011;17:1577–1584; doi:10.1038/nm.2531



Induction of lethal acute GVHD via nonhematopoietic APCs Graft-versus-host disease (GVHD) is a major cause of transplant-related mortality after hematopoietic stem cell transplantation. Although several studies have led to the assumption that recipient dendritic cells are the crucial cell type involved in initiation of GVHD, this has not been proven. In a study recently published in *Nature Medicine,* Koyama *et al* set out to determine the relative role of recipient antigen presenting cell (APC) subsets in inducing GVHD. To their surprise, they found that recipient nonhematopoietic APCs—specifically, intestinal myofibroblasts—were capable of inducing lethal major histocompatibility complex (MHC) class II–dependent GVHD. This is in contrast to MHC class I–dependent GVHD, which appears to be initiated by host hematopoietic cells. The fact that MHC class I– and class II–dependent GVHD appear to be initiated by different APCs provides a rationale for identifying an Achilles heel in the antigen-presenting pathway itself that can be exploited by targeted therapy.
Nature Medicine, published online 29 November 2011; doi:10.1038/nm.2597



Novel recurrent translocations in breast cancer Once considered the province almost exclusively of hematolymphoid neoplasms and sarcomas, chromosomal translocations and gene fusions are increasingly being recognized in epithelial cancers. To identify recurrent gene fusions in breast cancer, Robinson *et al*, as reported in a recent letter in *Nature Medicine,* performed next-generation paired-end transcriptome sequencing coupled with bioinformatics analysis. They found two classes of recurrent gene fusions, each in approximately 5% of breast cancers: one involving microtubule-associated serine–threonine (MAST) kinases, the other involving members of the Notch family. Both classes conferred oncogenic characteristics to breast epithelial cells *in vitro*, suggesting that they can participate in breast cancer pathogenesis. These studies highlight the power of next-generation sequencing for identifying rare cancer-associated translocations as well as for personalized cancer therapy.
Nature Medicine 2011;17:1646–1651; doi:10.1038/nm.2580