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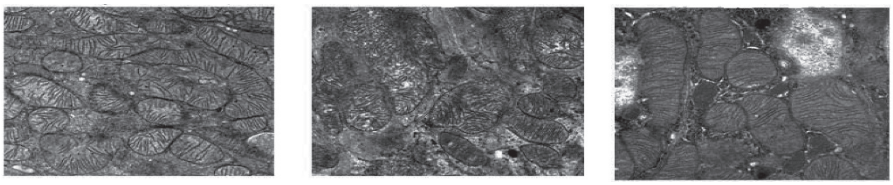

Regulation of tenofovir renal toxicity

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Advances in the treatment of individuals infected with HIV-1 have resulted in many patients leading relatively normal lives. However, they require maintenance therapy with antiretroviral compounds that inhibit viral replication. Tenofovir disoproxil fumarate (TDF) is a nucleotide analog of adenosine monophosphate that inhibits HIV-1 reverse transcriptase and has been very successful in controlling HIV-1. However, a subset of TDF-treated HIV-infected individuals develop acute renal failure. Because TDF is excreted by the kidney, Kohler and colleagues hypothesized that accumulation of TDF within renal proximal tubular cells led to toxicity and subsequent acute tubular damage/acute renal failure. They focused their attention on organic anion transporter 1 (OAT1), a member of a protein superfamily that transport a wide range of organic compounds and was suspected to be involved in uptake of TDF. They also examined the role of multidrug-resistant protein type 4 (MRP4), which is highly expressed in renal proximal tubules and was thought to mediate TDF efflux.

Using *Mrp4* and *OAT1* mouse knockout models, they demonstrated that *OAT1* is the major transporter responsible for TDF uptake; *OAT1* knockout mice did not develop renal toxicity after exposure to toxic levels of TDF. They also found that *Mrp4* knockout mice are more susceptible to TDF renal toxicity, presumably because absence of Mrp4 blocks TDF efflux, resulting in increased renal toxicity. Since only some patients develop TDF-treatment-related renal toxicity, these results suggest that OAT1 or MRP4 polymorphisms may be responsible. Further studies will be required to validate this hypothesis.

Combination therapy with tamoxifen and gemcitabine

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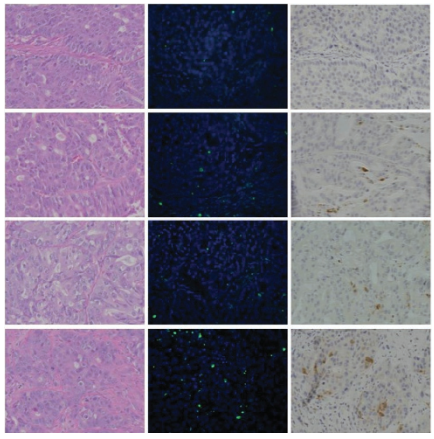
Cholangiocarcinoma is a malignant neoplasm that originates from cells with bile duct differentiation. In the past few years, its incidence and mortality have increased. Currently, cholangiocarcinoma is treated medically with gemcitabine, which has some activity. However, the overall prognosis is very poor, with a 5-year



survival of less than 5%. Intrahepatic cholangiocarcinoma has a median survival of 18–30 months. Clearly, new approaches to treat cholangiocarcinoma are needed. Tamoxifen has been shown to induce cell death in cholangiocarcinoma *in vitro* and *in vivo* in immunocompromised mice. Interestingly, cholangiocarcinoma cells do not express estrogen receptor; tamoxifen was therefore presumed to work through a mode of therapeutic action other than inhibition of estrogen receptor. Further work determined that the activity of tamoxifen was dependent on AKT signaling and FLIP expression. Given that gemcitabine has activity in cholangiocarcinoma, Jing *et al* asked whether tamoxifen might augment the clinical efficacy of gemcitabine in cholangiocarcinoma.

The authors found that tamoxifen did indeed boost the activity of gemcitabine both *in vitro* and *in vivo*. Tamoxifen enhanced the therapeutic effect of gemcitabine on tumorigenesis by 33% in an immunocompromised mouse xenograft model. Further studies showed that tamoxifen activated caspase 2 and 3—in contrast to gemcitabine, which activated only caspase 3. Inhibition of caspase 2 in cholangiocarcinoma cells treated with tamoxifen, but not gemcitabine, diminished caspase 3 activation, demonstrating that the ability to activate caspase 3 is at least partially dependent on caspase 2 in tamoxifen-treated cholangiocarcinoma cells. These results suggest that the combination of tamoxifen and gemcitabine will have greater clinical efficacy in the treatment of cholangiocarcinoma in comparison with gemcitabine monotherapy.

Mechanism of therapeutic resistance in endometrial carcinoma

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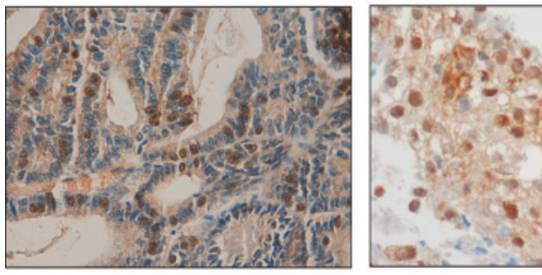
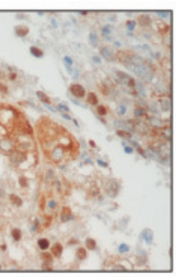
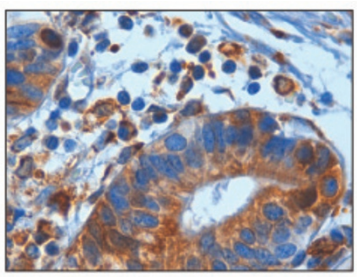
Endometrial carcinoma is the most common gynecologic cancer, with more than 35,000 cases in the United States each year. Surgery is the mainstay of therapy, but in some cases it is augmented by radiation therapy. However,



recurrences arise after radiation therapy, indicating that a subset of endometrial carcinomas are resistant to radiation therapy. Adaptation to hypoxia is a well-known mechanism of cancer resistance. Resistance is mediated by expression of hypoxia-inducible factor-1α (HIF-1α), a hypoxia-inducible transcription factor that targets a variety of genes to mediate cell survival during hypoxic states. Because HIF-1α has been linked to cancer cell survival during hypoxia, Yeramian *et al* wondered whether it might mediate therapeutic resistance in endometrial carcinoma.

The authors demonstrated that nuclear HIF-1α expression was increased in endometrial carcinoma recurrences that had been treated with irradiation, in contrast with primary endometrial carcinomas. Since nuclear factor-κB (NF-κB) is a cell-survival factor known to be activated by hypoxia, they also asked whether HIF-1α expression correlated with nuclear localization of NF-κB. They demonstrated that nuclear HIF-1α correlated with nuclear NF-κB. Furthermore, they showed that hypoxia activated NF-κB via both the canonical and alternative pathways of NF-κB activation in endometrial carcinoma cell lines. Finally, knockdown/depletion of either RelA (p65) central to the canonical NF-κB pathway or p100/52 central to the alternative NF-κB pathway decreased endometrial carcinoma cell survival under hypoxic conditions. These results demonstrate that HIF-1α-mediated activation of both the canonical and alternative NF-κB pathways is at least in part responsible for endometrial carcinoma survival during hypoxic stress.





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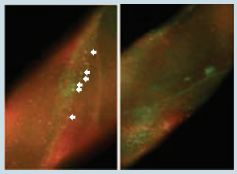
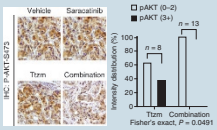
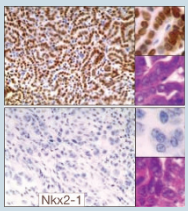


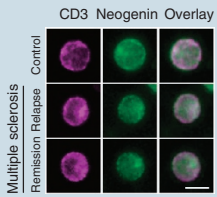
Lifespan expansion by maintenance of protein homeostasis Protein homeostasis is a critical contributor to long life span. As reported in a recent letter in *Nature*, Alavez *et al* asked whether treatment with compounds that bind to protein aggregates such as amyloid would extend life span in the nematode *Caenorhabditis elegans*. They found that thioflavin T (ThT), an amyloid binding dye that is used diagnostically in the detection of amyloid protein in tissue sections, prolonged the median life span by 60% and the maximal life span by 43–78%. Furthermore, ThT decreased protein aggregation–associated paralysis. Detailed examination of the mechanism led to the hypothesis that amyloid-binding compounds act as stress-response mimetics and activate stress-response pathways via transcription-factor activation, leading to stabilization of misfolded proteins. These results suggest that treatment with amyloid binding compounds will be useful in prolonging longevity and in the treatment of age-related diseases.
Nature 2011;472:226–229; doi:10.1038/nature09873



SRC activation is a unifying mechanism of trastuzumab resistance Trastuzumab—a humanized antibody that targets human epidermal growth factor receptor-2 (HER2 or ERBB2)—is used in the treatment of HER2-overexpressing breast cancers. There are diverse mechanisms of resistance in trastuzumab-resistant tumors. To develop a therapeutic option for patients with trastuzumab-resistant tumors, as described in a recent article in *Nature Medicine*, Zhang *et al* examined whether there might be a common protein that is activated in all trastuzumab-resistant breast cancers. They demonstrated that the nonreceptor tyrosine kinase c-SRC (SRC) was activated in trastuzumab-resistant breast cancers and that treatment with the SRC inhibitor saracatinib in combination with trastuzumab was effective in overcoming trastuzumab resistance. Given that saracatinib has been well tolerated in phase I and II trials, these results suggest that this combination is ready to move into clinical trials.
Nature Medicine 2011;17:461–469; doi:10.1038/nm.2309



Loss of thyroid transcription factor 1 is important in lung tumor progression Nkx2-1, also known as thyroid transcription factor 1, is a well-known immunohistochemical marker of pulmonary adenocarcinoma. However, Winslow *et al*, in a recent letter in *Nature*, explain how loss of Nkx2-1 is also responsible for promoting aggressive clinical behavior in pulmonary adenocarcinomas. Using genetically engineered mice, they showed that some metastatic adenocarcinomas lost Nkx2-1 and generally were more poorly differentiated than tumors that retained Nkx2-1 expression. They tied loss of Nkx2-1 to de-repression of Hmga2, an embryologically restricted regulator of chromatin structure. Finally, they provided evidence that loss of NKX2-1 expression and gain of HMGA2 expression were more often associated with moderately to poorly differentiated human pulmonary adenocarcinomas, validating the use of mouse models to identify important biological mechanisms that are relevant to human cancers.
Nature, published online 6 April 2011; doi:10.1038/nature09881



Activation of T cells in autoimmune encephalomyelitis Demyelination of white matter in the brain and spinal cord due to $CD4^+$ T cell–initiated inflammation is central to the pathogenesis of multiple sclerosis (MS). Repulsive guidance molecule-a (RGMa), originally identified as an axonal guidance molecule, was found by Muramatsu and colleagues in dendritic cells. In their recent article in *Nature Medicine*, they describe how this prompted them to ask whether RGMa might be involved in the pathogenesis of MS. They demonstrated that $CD4^+$ T cells express neogenin, a receptor for RGMa. In an experimental mouse model of autoimmune encephalomyelitis, neutralizing antibodies to RGMa reduced central nervous system inflammation and clinical symptoms. These results suggest that RGMa could be an excellent target for treatment of MS.
Nature Medicine 2011;17:488–494; doi:10.1038/nm.2321