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Resveratrol sensitizes cholangiocarcinoma to chemotherapy

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Cholangiocarcinoma is a notoriously chemotherapy-resistant tumor with a very poor prognosis; surgery is therefore the mainstay of treatment. Resveratrol, a naturally occurring compound found in red wine, grapes, and peanuts, has been touted as having health benefits, including a role in cancer prevention. It has been shown to downregulate the expression and activity of cytochrome p450 1b1 (Cyp1b1), a metabolic enzyme, in several cell lines. Cyp1b1 is overexpressed in several cancers and is known to mediate resistance to flutamide via inactivation in prostate cancer. On the basis of these data, Frampton *et al* wondered whether inactivation of Cyp1b1 by resveratrol might sensitize cholangiocarcinoma cells to current therapies.

The authors demonstrated that resveratrol was active as a single agent and, more importantly, that at low doses it sensitized cholangiocarcinoma cells to 5-fluorouracil (5-FU), mitomycin C, and gemcitabine. Furthermore, the combination of resveratrol and 5-FU decreased tumor growth and increased tumor latency in a mouse

cholangiocarcinoma xenograft model, as compared with 5-FU alone. The combination also appeared to have low toxicity. In seeking to better understand the mechanism of action of resveratrol in this context, they found that resveratrol decreased the expression of Cyp1b1 and that depletion of Cyp1b1 by short hairpin RNA sensitized cholangiocarcinoma cells to various chemotherapies similarly to the combination of resveratrol and various chemotherapies both *in vitro* and *in vivo*. Overall, these results suggest that resveratrol may be useful to sensitize cholangiocarcinoma to standard chemotherapy in humans. Clearly, further studies—and possibly clinical trials—are warranted to test this interesting new therapeutic opportunity.

Involvement of MMP2 in the pathogenesis of diabetic retinopathy

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Diabetic retinopathy is the most common cause of adult blindness. Oxidative stress due to elevated glucose levels is thought to play a major role in the development of diabetic retinopathy, but the exact mechanism is not clear. Previous work has shown that matrix metalloproteinase-2 (MMP2), which cleaves collagen type IV,

is under the control of superoxide and is crucial to the pathogenesis of diabetic retinopathy. To further investigate the link between MMP2 and this disorder, Mohammad and Kowluru tested the hypothesis that superoxide leads to MMP2 activation, which subsequently induces mitochondrial dysfunction and retinal capillary endothelial cell apoptosis.

The authors observed that high glucose levels led to elevated reactive oxygen species and increased MMP2 activity in endothelial cells. These were accompanied by mitochondrial swelling and apoptosis. Depletion of MMP2 by small interfering RNA reduced these glucose-mediated

cellular changes. Utilizing a mouse model that overexpressed mitochondrial superoxide dismutase, Mohammad and Kowluru demonstrated a reduction of diabetes-induced activation of MMP2. Their data suggest a model wherein MMP2 inhibition lessens glucose-induced mitochondrial superoxide and mitochondrial dysfunction, resulting in inhibition of capillary endothelial cell apoptosis. These results indicate that targeted inhibition of MMP2 could be a reasonable strategy for the prevention of diabetic retinopathy.

The role of c-MET activation in diffuse large B-cell lymphoma

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Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma in adults, accounting for approximately

30–40% of all cases of non-Hodgkin lymphoma. Although DLBCL responds well to multimodal therapy, approximately 50% of patients eventually succumb to the disease. c-MET is the hepatocyte growth factor receptor, a receptor tyrosine kinase that is involved in the pathogenesis of several neoplasms. c-MET is known to be expressed in germinal-center B cells and on terminally differentiated plasma cells, and it is also known to be involved in the pathogenesis of DLBCL. Because c-MET is a receptor tyrosine kinase, it is an attractive therapeutic target. To assess the importance of c-MET in the pathogenesis of DLBCL, Uddin *et al* performed an analysis of c-MET expression and determined the effects of its inhibition on proliferation and apoptosis.

The authors showed that approximately 70% of DLBCL expressed c-MET at high levels and that c-MET expression was significantly more common in the germinal-center subtype of DLBCL. Surprisingly, c-MET expression was associated with a better prognosis. Uddin and colleagues found that activation of c-MET by hepatocyte growth factor increased proliferation and inhibited apoptosis, whereas inhibition of c-MET, by either a pharmacological inhibitor or small interfering RNA knockdown, resulted in decreased signaling through AKT, decreased proliferation, and a concomitant increase in apoptosis. These results suggest that pharmacological inhibition of c-MET might be of utility in the treatment of c-MET-expressing DLBCL.

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Gene signature predicts prognosis in sarcomas

Non-translocation-related sarcomas are the most frequent sarcomas in adults. Currently, the College of American Pathologists advocates sarcoma grading according to the Fédération Française des Centres de Lutte Contre le Cancer system, which is based on histologic criteria. To take an alternative approach to predicting prognosis in non-translocation-related sarcomas, Chibon *et al*, as recently reported in *Nature Medicine*, performed genomic profiling of a group of sarcomas and identified a group of genes that they termed CINSARC (complexity index in sarcomas)—genes involved in mitosis and chromosomal management that were lost or gained with increasing frequency in more aggressive sarcomas. Interestingly, because control of mitosis and chromosomal integrity are common to all neoplasms, the CIN-SARC profile also predicted prognosis in a variety of other cancers.

Nature Medicine 2010;16:781–787; doi:10.1038/nm.2174

Vaccine for prophylaxis and treatment of breast cancer

In a recent letter in *Nature Medicine*, Jaini and colleagues hypothesized that a full-strength autoimmune attack sufficient to induce organ-specific failure may provide protection and therapy against tumors derived from the targeted organ. To test this hypothesis, they immunized mice with α -lactalbumin, a breast-specific protein that is expressed in lactating, but not nonlactating, mammary tissue. They found that lactating mice that had been immunized with α -lactalbumin, but not controls, developed breast failure. They also showed that mice that had been immunized with α -lactalbumin failed to develop breast cancer in a mouse mammary tumor virus model and that tumor growth was inhibited in a transplantable breast cancer model. The authors emphasize that this same general strategy could be used to develop cancer vaccines for prophylaxis and treatment of cancers specific to other organs.

Nature Medicine 2010;16:799–803; doi:10.1038/nm.2161

Engineering a transplantable liver

There is a shortage of suitable livers for transplantation of patients with liver failure. To bypass this limitation, Uygun *et al*, in a recent technical report in *Nature Medicine*, propose engineering livers from decellularized livers that are otherwise unsuitable for trans-

plantation. They describe a technique to make a recellularized liver from a decellularized liver matrix. By perfusing rat livers with sodium dodecyl sulfate, they achieved a decellularized liver matrix that retained the shape of the liver as well as extracellular matrix proteins. They showed that the decellularized matrix could be recellularized by hepatocytes that retained various functional parameters and that brief transplantation of the recellularized livers was feasible. However, to generate a functional liver, it will be necessary to engineer grafts with endothelial cells, stellate cells, biliary epithelial cells, and Kupffer cells in addition to hepatocytes.

Nature Medicine 2010;16:814–820; doi:10.1038/nm.2170

Disturbance of circadian clock linked to hypoin-sulinemia and diabetes

The circadian clock drives cycles of energy storage and utilization in anticipation of changes in the rising and setting of the sun. In humans, one of the most pronounced circadian cycles involves the daily variation of glucose tolerance and insulin sensitivity, which is disrupted in type 2 diabetes. To elucidate the relationship between insulin secretion and the circadian clock, Marche *et al*, as reported in a recent letter in *Nature*, examined glucose metabolism and insulin secretion in mice deficient in core circadian clock components. They showed that mice harboring a pancreas-specific deletion of the circadian clock led to a defect in insulin secretion and type 2 diabetes, confirming an important role for the pancreatic circadian clock in coordinating insulin secretion with the sleep–wake cycle.

Nature 2010;466:627–631; doi:10.1038/nature09253