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Potential therapy for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, but, as a testament to its aggressiveness, it is the third most common cause of cancer-related deaths. The only US Food and Drug Administration–approved chemotherapy for HCC is sorafenib, a small-molecule tyrosine kinase inhibitor that prolongs the life of advanced HCC patients by about 3 months. New therapies are sorely needed to treat this aggressive cancer. Imidazolium salts (IMSs) are organic compounds that are routinely used as ligands or organocatalysts in synthetic chemistry. Recently, several IMSs have been shown to have antifibrotic and antioxidative properties. In the work reported in this issue, Gopalan *et al.* examined whether IMSs might have anti-HCC activities.

The authors found that a subset of IMSs had potent antiproliferative activity in several HCC cell lines without being toxic to noncancerous liver, breast, and lung cell lines, suggesting that the compounds were relatively nontoxic. Further analysis revealed that cells treated with the IMSs were arrested during the G1 phase of the cell cycle, apparently as a result of decreased expression levels of cell cycle regulatory proteins. Analysis of IMSs in

a mouse xenograft HCC model revealed that one IMS resulted in a 45% and 60% decrease in tumor volume at doses of 0.6 and 1.5 g/l doses, respectively, after 3 weeks of treatment. The decrease in tumor size was accompanied by increased apoptosis. While these studies highlight IMSs as a novel class of compounds with anti-HCC activities, the authors acknowledge that further work needs to be done to establish the anti-HCC activities across other animal models, including genetically engineered and orthotopic mouse HCC models.

Statin-induced angiogenesis during ischemia

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Statins were developed to lower plasma cholesterol by inhibiting HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway responsible

for cholesterol synthesis. As a class, these drugs are extremely effective and have revolutionized the treatment of hypercholesterolemia, resulting in many billions of dollars of sales each year. Additionally, these drugs have pleiotropic effects on enzymes beyond HMG-CoA reductase, which have added benefits, including the prevention of ischemic heart disease. Because statin administration has been reported to increase blood flow recovery in ischemia models, Kikuchi and colleagues investigated the mechanism of blood flow recovery in a murine hindlimb ischemia model after administration of pitavastatin.

The authors demonstrated that classic vascular endothelial growth factor (VEGF) signaling was not involved in the increase in blood flow because VEGF, Flt-1, and Flk-1 expression was unaltered after administration. However, they found that Notch signaling was increased by activating phosphatidylinositol-3 kinase (PI3K)/Akt signaling and γ -secretase activity. Notch signaling is known to be an important mediator of arteriogenesis and angiogenesis. γ -Secretase is required to activate Notch signaling by cleaving Notch1 to liberate the active intracellular domain, whereby it can interact with the RBP-J protein in a complex to activate nuclear transcription of proangiogenic genes. Further *in vitro* modeling demonstrated that pitavastatin-induced Notch signaling led to increased endothelial proliferation and increased angiogenesis *in vitro* and *in vivo*. Overall, the authors' findings indicate that pitavastatin increases blood flow through increased arteriogenesis and angiogenesis mediated by increased Notch signaling.

Mechanism of metastasis induced by MUC1 in esophageal carcinoma

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Esophageal squamous cell carcinoma (ESCC) is a common form of esophageal carcinoma that is associated with a poor

prognosis because it usually presents with advanced-stage disease. Lymph node metastasis is common and is also associated with a poor prognosis. Recently, it has been found that elevated expression of MUC1, a transmembrane mucin, is linked to advanced-stage and lymph node metastasis, suggesting a mechanistic relationship between MUC1 expression and metastasis. Expression of matrix metalloproteinase 13 (MMP13), a proteolytic enzyme, also correlates with vascular invasion and lymph node metastasis in ESCC. To further understand the mechanism of metastasis in ESCC, Ye and colleagues asked whether there is a mechanistic relationship between MUC1 and MMP13.

By studying a cohort of patients with localized or metastatic ESCC, the authors found that expression of both MUC1 and MMP13 exhibited a statistically significant positive correlation with lymph node metastasis. They used a luciferase reporter assay to determine that MUC1 expression stimulated expression of MMP13. After dissecting the MMP13 promoter, they discovered that a Runx-2 binding site was essential for stimulating MMP13 expression. Runx-2 is a transcription factor known to play important roles in skeletal morphogenesis, and it is involved in the pathogenesis of numerous cancers. The authors showed that expression of MUC1 in rat fibroblasts led to increased migration, invasion, and adhesion that could be rescued by expression of MMP13. They thus demonstrated that MUC1 regulates migration, invasion, and adhesion through expression of MMP13. This study highlights MUC1 as a possible therapeutic target in ESCC.

Novel regulatory mechanism of p53 The *TP53* tumor suppressor gene is frequently mutated in human cancer cells. Control of p53 plays a crucial role in normal cell function and tumorigenesis. Several types of tumors, such as medulloblastomas and ependymomas, do not harbor inactivating *TP53* mutations, suggesting alternative mechanisms of regulating p53. In a recent article in *Nature Medicine*, Wu *et al* asked whether ubiquitination factor E4B (UBE4B), an E3 and E4 ubiquitin ligase, might be able to target p53 for ubiquitin-mediated degradation. They found that UBE4B forms a complex with p53 and Hdm2, leading to polyubiquitination of p53 and degradation. To validate their results in a human tumor, they showed that brain tumors that lacked *TP53* mutations or overexpression of MDM2 showed amplification and overexpression of *UBE4B*, thus providing a novel mechanism for inactivation of p53.

Nature Medicine 2011;17:347–355; doi:10.1038/nm.2283

Mechanism of mitochondrial dysfunction in Huntington's disease Huntington's disease is an incurable neurodegenerative disease caused by a mutant form of huntingtin, which is encoded by *HTT*

and contains an abnormal polyglutamine expansion. One hypothesis regarding the pathogenesis of mutant *HTT* suggests that mitochondrial dysfunction characteristic of Huntington's disease is caused by defects in mitochondrial fission–fusion equilibrium. This hypothesis was evaluated in a recent letter in *Nature Medicine* by Song *et al*. They demonstrated that mutant huntingtin sways the fission–fusion balance, leading to mitochondrial fragmentation both *in vitro* and *in vivo*. The mechanism of action appears to be through abnormal binding of the mitochondrial fission GTPase dynamin-related protein-1 (DRP1), which stimulates its enzymatic activity. This is potentially good news for Huntington's patients because DRP1 could be useful to target therapeutically to prevent neurodegeneration in patients with Huntington's disease.

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Surprising interaction between XBP-1 and FoxO1 regulates glucose homeostasis X-box-binding protein-1 (XBP-1s) is known to act as a transcription factor to regulate endoplasmic reticulum (ER) folding capacity. XBP-1s is also known to regulate glucose homeostasis, which has previously been attributed to its ability to regulate ER folding capacity. FoxO1, a forkhead transcription factor, is also known to play critical roles in glucose homeostasis. Considering the important roles for XBP-1s and FoxO1 in glucose homeostasis, Zhou *et al*, as reported in a recent article in *Nature Medicine*,

asked whether XBP-1s directly affected FoxO1. To their surprise, they found that, independent of its ability to regulate ER stress, XBP-1s directly bound FoxO1 to promote its degradation through the 26S proteasome pathway. These results have profound implications for the pathogenesis of diabetes and lay the groundwork for XBP-1s-based diabetes therapy.

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A new aging model based on iPSCs Hutchinson–Gilford progeria syndrome (HGPS) is characterized by accelerated and premature aging and thus has the potential to provide insight into normal aging. To develop a model of HGPS, Liu *et al*, as described in a recent letter in *Nature*, came up with the ingenious idea to make induced

pluripotent stem cells (iPSCs) from fibroblasts of HGPS patients and then ask whether the iPSCs showed features of aging after differentiation. They found that iPSCs derived from fibroblasts of HGPS patients did not express progerin, the mutant form of the lamin A gene (*LMNA*) characteristic of HGPS or display cytomorphologic features associated with aging. However, when the HGPS-derived iPSCs were differentiated *in vitro*, they expressed progerin and displayed various hallmarks of aging. This *in vitro* system should be an invaluable model in which to study aging.

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