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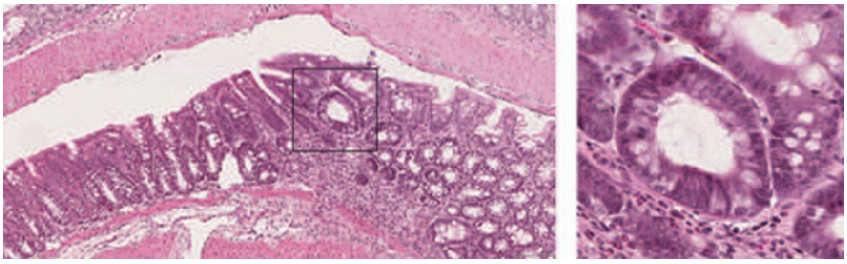

Lack of MMP10 exacerbates colitis and dysplasia

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Ulcerative colitis (UC) is characterized by chronic inflammation and the development of dysplasia and eventually colonic adenocarcinoma in some patients. Matrix metalloproteinases (MMPs) were originally thought to be excellent therapeutic targets for UC because the ulcers characteristic of UC are loaded with various MMPs. However, clinical use of MMPs lost traction when cancer trials with MMP inhibitors produced negative results. In light of such results in cancer trials, the roles of MMPs were reassessed, and, not surprisingly, it was determined that MMPs had myriad biological effects that are achieved by cleaving different substrates. In particular, they were found to have both pro- and anti-inflammatory and oncogenic effects. Researchers in the field appear to have shifted to a more focused dissection of the various effects of MMPs. MMP10 (also known as stromelysin-2) is expressed strongly at the edges of healing ulcers in UC patients.

Koller *et al* systematically examined the role of MMP10 in a mouse model that approximates many of the features of human UC. Using MMP10 knockout mice, they discovered that inflammation caused by ingestion of dextran sodium sulfate was prolonged. These mice also had increased numbers of dysplastic lesions. Because UC patients are at increased risk for the development of colon cancer, the results suggest that MMP10 inhibition could lead to an increase in the incidence of UC-related dysplasia/cancer. It is not clear whether increasing the level of MMP10 would decrease inflammation and colonic dysplasia, but the results of this study suggest that this might be worth trying.

Seeing tissue at microscopic resolution with sound

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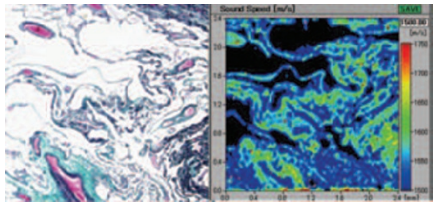

Conventional light microscopy using hematoxylin and eosin (H&E) as well as numerous specialized staining procedures has been extremely useful in diagnosing and understanding a variety of diseases. However, there are those who are not satisfied with conventional light microscopy and are working to develop alternatives. A scanning acoustic microscope (SAM) uses ultrasound to image tissue. The principles seem very simple: the "harder" the tissue, the faster sound travels. Apparently, "hardness" depends on collagen/muscle fibers or cell density. Differences in how fast the sound travels are deconvoluted into beautiful images that are similar in quality to H&E-stained sections. Proponents of SAM cite the following advantages: (i) the images are acquired in only a few minutes, (ii) staining the tissue is not necessary, and (iii), the speed of sound is recorded digitally so the image data can be analyzed statistically, allowing numerical comparisons between different tissues and disease states.

Noting that no one had reported using SAM to image pulmonary tissue, Miura and Yamamoto applied the technique in a variety of pulmonary diseases. They captured stunning images of formalin-fixed paraffin-embedded tissue sections. In addition, they compared SAM images with conventional H&E images. SAM images are very pretty, with 'harder' tissues appearing more red and 'softer' tissues appearing more blue. It is relatively easy to discriminate diseases using SAM images. The authors note that they can even discriminate between usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) because the sound speed was significantly greater for UIP than for NSIP. In addition, the authors point out that SAM can be used to examine virtually any tissue and disease.

Lumican is integral to hepatic fibrosis

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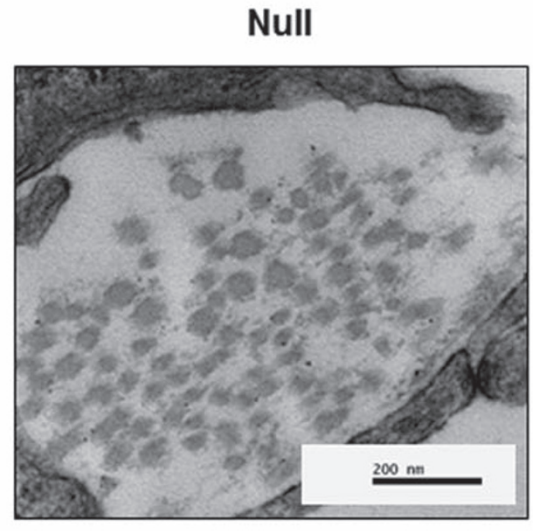
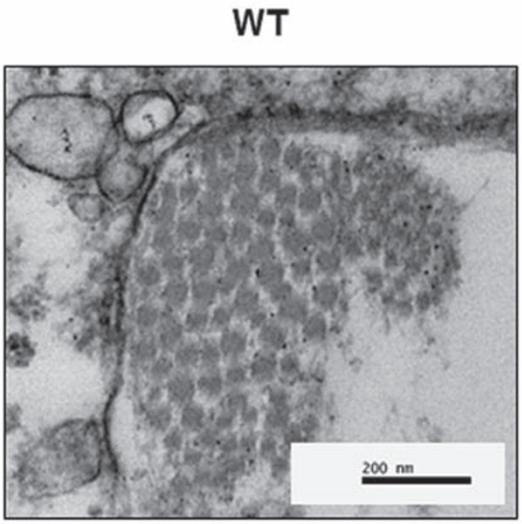
A member of the small leucine-rich family of proteoglycans (SLRPs), lumican has been studied extensively. It is involved in collagen fibril assembly; lumican knockout mice have fragile skin and cloudy corneas with thick or irregular collagen fibrils. In addition, lumican has been implicated in cellular functions, including angiogenesis, cell-cycle initiation, cell proliferation, cell



migration, Toll-like receptor 4 signaling, and Fas-mediated immune activation. Recently, lumican was found to be significantly overexpressed in the hepatic proteome of nonalcoholic steatohepatitis (NASH) livers. Krishnan *et al* therefore speculated that it might be involved in the pathophysiology of NASH and other hepatic diseases that cause fibrosis. They also hypothesized that lumican deficiency may protect against hepatic liver injury and fibrosis.

The authors found that lumican was upregulated in several hepatic diseases in mouse models and in human liver lesions. When they examined a lumican knockout mouse in a carbon tetrachloride hepatic injury model, they discovered that, although the knockout mice were not protected against the initial injury, they failed to develop as much hepatic fibrosis as wild-type controls did. Further experiments showed an increase in matrix metalloproteinase 13 (MMP13), which is known to degrade collagen. Electron microscopy revealed that the collagen fibrils in lumican knockout livers were poorly organized. Overall, these findings indicate that lumican maintains collagen stability; its deficiency contributes to increased collagen degradation by MMP13 and decreased collagen assembly. The study therefore suggests that targeting lumican therapeutically could lessen hepatic fibrosis in various disorders that affect the liver.



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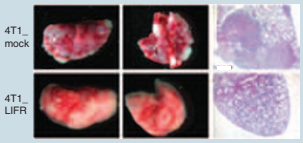
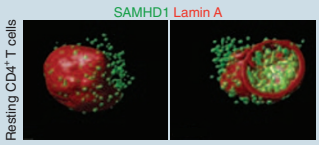
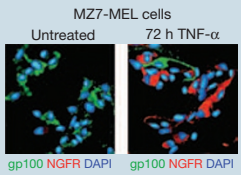


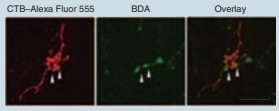
Suppression of metastasis by LIFR microRNA-9 (mir-9) is known to inhibit metastasis through the targeting of E-cadherin. In a recent article in *Nature Medicine*, Chen *et al* demonstrated that mir-9 also targets leukemia inhibitor factor receptor (LIFR). They showed that LIFR acts as a metastasis suppressor. Mechanistically, it activates the Hippo pathway, a conserved pathway that regulates cell size and has been implicated in cancer. They found that LIFR forms a complex with known members of the Hippo kinase cascade, leading to inactivation of the effector protein YAP. Thus, downregulation of LIFR activates YAP, promoting metastasis. The authors' evaluation of clinical breast cancer specimens revealed that loss of LIFR correlated with metastasis and determined prognosis. These results suggest that loss of LIFR is a biomarker for metastasis prognosis and that reactivation of LIFR might suppress metastasis.
Nature Medicine 2012;18:1511–1517; doi:10.1038/nm.2940



SAMHD1 restricts HIV-1 infection in resting CD4$^+$ T cells Unlike activated CD4$^+$ T cells, resting CD4$^+$ T cells resist infection by HIV-1. However, until now, the mechanism behind this resistance had remained elusive. As described in a recent letter in *Nature Medicine*, Baldauf *et al* discovered that the deoxynucleoside triphosphate triphosphohydrolase SAMHD1 is responsible. SAMHD1 enzymatically depletes deoxynucleotide triphosphates (dNTPs) in the cytoplasm that are required for reverse transcription. The authors hypothesize that regulation of deoxynucleotide levels in resting cells by SAMHD1 may have evolved to protect T helper cells from retroviral infection without disrupting the homeostasis of these noncycling cells. On the basis of these results, they propose that manipulation of intracellular dNTP pools could be a therapeutic strategy for HIV-1.
Nature Medicine, published online 12 September 2012; doi:10.1038/nm.2964



How melanomas resist T-cell therapy Adoptive cell-transfer therapies (ACTs) can achieve remission in melanoma patients, but they frequently relapse. To elucidate the mechanism of relapse, Landsberg *et al* established a mouse melanoma ACT therapy model, as reported in a recent letter in *Nature*. They demonstrated that inflammatory cells induce dedifferentiation in melanoma cells via inflammatory mediators such as tumor necrosis factor-α. Dedifferentiation caused melanoma cells to lose the melanoma antigens that the therapy was directed against, thus allowing evasion of ACT. A fascinating aspect of the work is that the cells exhibited great plasticity as the researchers were able to coax them to re-express their melanoma antigens. Hence, the authors propose that future ACT protocols simultaneously target both melanocytic and nonmelanocytic antigens to ensure broad recognition of both differentiated and dedifferentiated melanoma cells.
Nature 2012;490:412–416; doi:10.1038/nature11538



Blood vessels talk to neurons during neuronal remodeling Angiogenesis is a general feature of several central nervous system (CNS) conditions, including multiple sclerosis (MS), brain tumors, epilepsy, and stroke. Therefore, targeting angiogenesis has been thought to be beneficial. However, inhibiting angiogenesis has the potential to impair wound healing and other repair processes. To ascertain whether angiogenesis might contribute to CNS repair, Muramatsu *et al*, as recently described in *Nature Medicine*, examined the role of angiogenesis in restoration of CNS function in an experimental mouse MS model. They found that endothelium within blood vessels secretes prostacyclin, which binds to the prostaglandin receptor on neurons, promoting the sprouting of neurons and contributing to the repair process. These results suggest that the strategy of inhibiting angiogenesis in conditions such as MS should be approached with caution because it might interfere with healing.
Nature Medicine, published online 7 October 2012; doi:10.1038/nm.2943