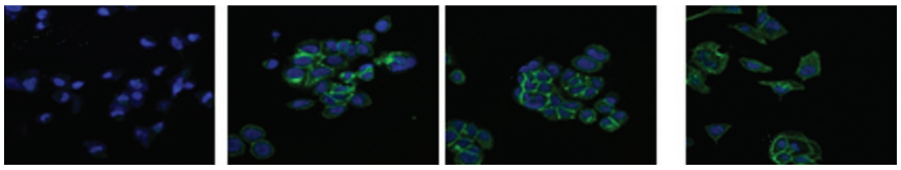
**Laboratory Investigation (2009) 89**, 1190-1191
© 2009 USCAP, Inc All rights reserved 0023-6837/09 $32.00

# INSIDE LI

doi:10.1038/labinvest.2009.114



## New tumor suppressor in breast cancer

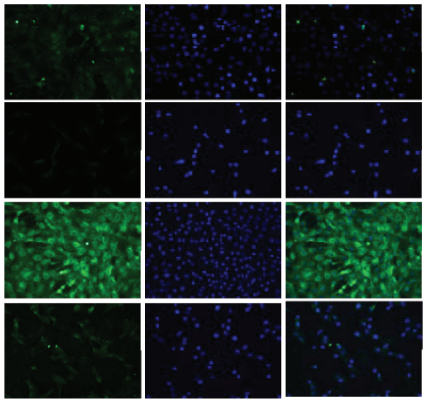
See page 1229

Endoplasmic reticulum (ER) stress plays an important role in initiating tumor cell quiescence. Recently, ER protein 29 (ERp29), which is targeted to the ER lumen, has been implicated in negatively regulating breast cancer cells and is therefore thought to serve a tumor-suppressive function. Expression of ERp29 correlates with more indolent cancer cell behavior.

To further investigate the roles of ERp29 in breast cancer, Bambang and colleagues performed a detailed *in vitro* and *in vivo* study. Initially, they studied a group of breast cancers and found that ERp29 was expressed at lower levels in breast cancers than in normal control tissues, and that ERp29 expression correlated inversely with aggressive behavior. Subsequently, they sought to understand the molecular pathogenesis of ERp29's suppression of breast cancer. They found that enforced expression of ERp29 induced cell-cycle arrest in breast cancer cell lines. Furthermore, expression of ERp29 resulted in morphologic changes suggestive of a mesenchymal–epithelial transition which was confirmed by molecular markers. Breast cancer cells expressing ERp29 also exhibited decreased cell motility, invasion, and ability to grow in soft agar or as xenografts. In aggregate, these results indicate rather broad roles of ERp29 in tumor suppression. Future experiments are needed to clarify the mechanism by which ERp29 mediates these varied functions. Nonetheless, it is clear that ERp29 is an important regulator of cellular behavior, and studies into the function of ERp29 are likely to yield significant insight into the biology of cancer.

## Spicy recipe for inhibition of hepatic fibrosis

See page 1275



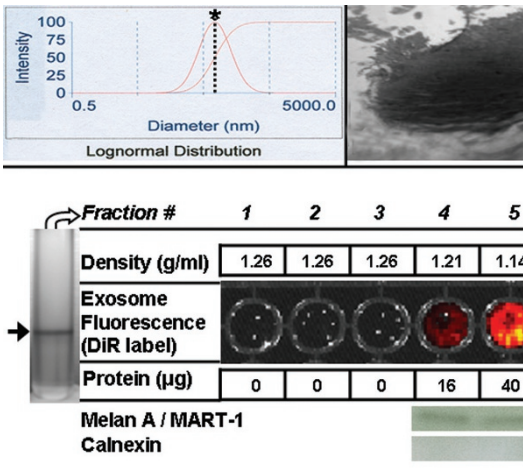
Type II diabetes mellitus (T2DM) has been steadily on the rise owing to changes in diet and lack of physical activity. The complications of T2DM are responsible for considerable morbidity and mortality. One such complication is nonalcoholic steatohepatitis (NASH). Up to one-third of NASH cases are associated with hepatic fibrosis and even cirrhosis. Both T2DM and NASH are associated with increased levels of low-density lipoprotein (LDL) and oxidized LDL (ox-LDL), implicating them in the pathogenesis of T2DM and NASH. Hepatic fibrosis is mediated by hepatic stellate cells (HSCs), which undergo a transformation upon activation, resulting in fibrosis. It has previously been shown that curcumin—a natural component of the spice turmeric, which has various uses in medicine—inhibits HSC activation.

Kang and Chen have further investigated the mechanism of action of curcumin in suppressing HSC activation. They found that LOX-1, a scavenger receptor for ox-LDL, is critical in importing ox-LDL into HSCs, resulting in HSC activation. Detailed analysis of transcriptional mechanisms controlling LOX-1 expression revealed that Wnt signaling is important in activating LOX-1 expression through peroxisome proliferator-activated receptor-γ (PPARγ) and that PPARγ is a target of curcumin. Interestingly, this study highlights the possible role of curcumin in prevention of ox-LDL-induced hepatic fibrosis and possibly other ox-LDL-induced diseases. Finally, this study should make us all want to eat more turmeric—pass the curry, please!

## How tumors talk to the microenvironment

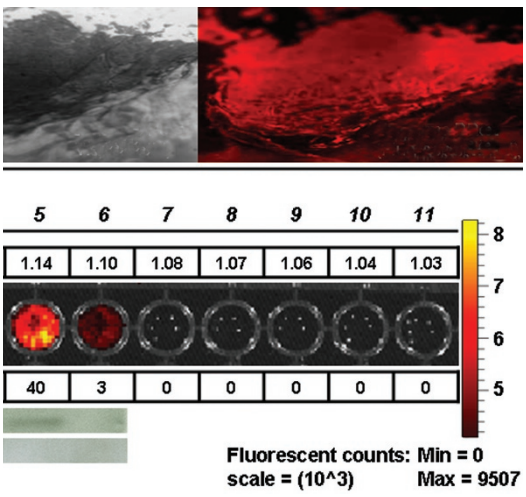
See page 1317

Communication between tumor cells and the microenvironment has been an area of intense study. Recently, attention has been focused on exosomes, nanoscale membrane fragments that are formed by inward budding of microvesicular bodies (MVBs), a component of the endocytic pathway. Exosomes are released into the surrounding microenvironment by fusion of MVBs with the plasma membrane, where they are able to gain access to the circulation. Because exosomes can contain proteins or nucleic acids

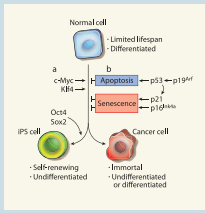


produced by tumor cells, they have the potential to influence cells within the microenvironment, once they deliver their contents. The nanoscale size of exosomes facilitates their penetration and interaction with the microenvironment.

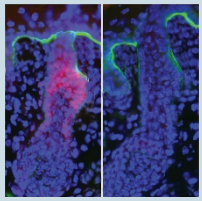
To examine the potential for exosomes to interact with endothelium, Hood and colleagues developed a novel *in vitro* 3D angiogenesis assay system. They also refined the technique for isolating exosomes, which incorporated dynamic light scattering. Furthermore, they were able to incorporate fluorescent or infrared dyes, which allowed them to visualize the exosomes. Using exosomes isolated from a melanoma cell line, the authors found that the exosomes localized to complex networks called tunneling nanotubule networks (TNTs). They hypothesized that TNTs might facilitate intercellular communication between target endothelial cells. They showed that exosomes promoted sprouting of endothelial structures at low doses and endothelial proliferation at higher doses. Further studies will be required to identify the contents of the exosomes that mediate the effects seen in the angiogenesis system. However, the authors present a plausible scenario for how tumor cells might prepare distant sites for the arrival of metastatic cells, thus enhancing their survival after metastasis.




# nature.com/pathology

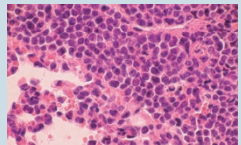



**Intriguing similarities between iPS and cancer cells** Induced pluripotent stem (iPS) cells hold tremendous promise for regenerative therapies. Yet the more we learn about them, the more reason there is for caution. In a recent News and Views item in *Nature*, Krizhanovsky and Lowe explore the emerging similarities between iPS and cancer cells. Like cancer cells, iPS cells require the expression of oncogenes such as *c-Myc* and *Klf4*, and, as has recently been discovered by several laboratories, inactivation of p53 enhances the efficiency of iPS-cell production. p53 is known to promote cell-cycle arrest or senescence of cells containing damaged DNA, and loss of p53 is a hallmark of many cancers. This raises the issue that loss of p53 or a functional equivalent might be required to generate iPS cells, which has obvious implications in terms of their ability to form cancers once they are transplanted. While much progress has been made in a very short time, there is clearly much to do before iPS cells can be used to treat human disease.
*Nature* 2009;460:1085–1086; doi:10.1038/4601085a



**Maintenance of skin epithelium** The Tcf family of proteins is known to bind β-catenin and transactivate Wnt target genes and to play important roles in skin development. In a recent article in *Nature Genetics*, Nguyen and colleagues studied the roles of Tcf3 and Tcf4 in skin development, repair, and maintenance. Using genetically engineered mice and ingenious skin grafting experiments, they uncovered critical roles for Tcf3 and Tcf4 in the maintenance of skin epithelial stem cells. Furthermore, they found an important function for Tcf3 and Tcf4 in epidermal homeostasis. Interestingly, some phenotypes appeared to be independent of β-catenin; this suggests that Tcf3 and Tcf4 have both Wnt-dependent and -independent functions. The authors suggest that Tcf proteins might function as transcriptional repressors when β-catenin is low or absent. Further studies will be required to test this hypothesis.
*Nature Genetics*, published online 30 August 2009; doi:10.1038/ng.431

**Circumventing MEK inhibition in Ras-activated leukemias** Tumors with inactivated *Nf1* result in deregulation of Ras and activation of the Raf, mitogen-activated protein kinase kinase (MEK), and extracellular signal-regulated kinase (ERK) pathway. The Raf-MEK-ERK pathway is thus an attractive pathway to target therapeutically in cancers with loss of *Nf1*. In a recent letter in *Nature*, Lauchle and co-workers investigated mechanisms of resistance to MEK inhibition in a mouse model of *Nf1*-deficient acute myeloid leukemia. Using a retrovirus-based insertion mutagenesis strategy, they identified activation of RasGRP1 and reduction of p38α (MEK) activity as mechanisms of resistance to MEK inhibition. Together, these results suggest that there is a finely tuned level of MEK activation that results in sensitivity to MEK inhibition, indicating that reliance on MEK inhibition alone is a questionable therapeutic strategy in Ras-activated cancers.
*Nature* 2009;461:411–414; doi:10.1038/nature08279



**Molecular mechanism of epilepsy** Autosomal dominant lateral temporal lobe epilepsy (ADLTE) is characterized by frequent partial seizures and generalized tonic–clonic seizures approximately once per year. Recently, *LGI1* was identified as the gene responsible for this disorder. *LGI1* encodes a 64-kDa secreted protein that localizes to glutamatergic synapses. To understand the role of *LGI1* in epilepsy, Zhou and colleagues, as described in a recent article in *Nature Medicine*, generated transgenic mice expressing a C-terminal truncated form of a protein (mLGI1) that reproduced a human ADLTE mutation. They found abnormal postnatal neuron development that resulted in increased excitatory synaptic transmission and kindling epileptogenesis *in vivo* after γ-aminobutyric acid$_A$ receptor blockade. On the basis of their results, they propose that mLGI1 has a dominant negative mode of action that acts to disrupt postnatal development in early childhood and thereby to promote epilepsy throughout life.
*Nature Medicine*, published online 23 August 2009; doi:10.1038/nm.2019