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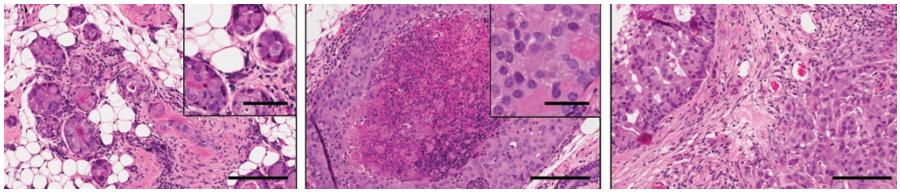

Human cell lines for studying breast cancer progression

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Histological evaluation of breast specimens has revealed specific morphologic findings associated with each stage in the evolution of breast cancer. Specifically, there are characteristic morphological findings associated with normal breast tissue, atypical ductal hyperplasia (ADH), ductal carcinoma *in situ* (ADH), and invasive mammary carcinoma (IMC). Histological characterization of these different stages of breast cancer has facilitated molecular analysis by expression arrays and proteomics, which have identified numerous candidate disease-specific and therapeutic targets. However, *in vitro* live cell systems are necessary to validate the findings from these studies. Recognizing the need for such a system, Souter *et al* have validated the 21T series cell lines. These lines, derived from a single patient, have been proposed to represent the spectrum of breast neoplasia from ADH to IMC. The 21PT and 21NT cell lines were established from a mastectomy specimen and correspond to ADH and ductal carcinoma *in situ*, respectively. 21MT-1, corresponding to IMC, was obtained from a malignant pleural effusion. Characterization of these lines showed that they indeed show the histologic hallmarks of their disease-specific stages when grown in the mammary fat pads of nude mice. Importantly, they retained these characteristics when grown in three-dimensional Matrigel cultures. RNA expression analysis of the three lines revealed stage-specific gene expression patterns. The system also provides a platform for identifying the stage-specific genes that actually promote tumor progression, thereby highlighting them for targeted therapy.

Dissection of early events in enterohemorrhagic *E. coli* infection

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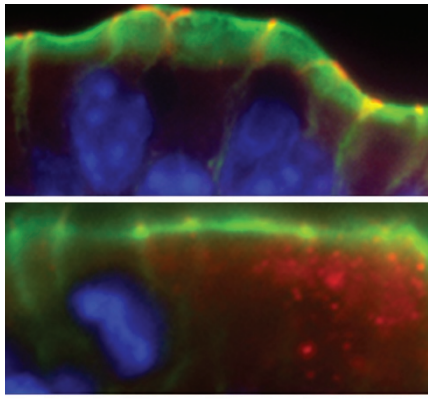
Enterohemorrhagic *Escherichia coli* (EHEC), a major cause of foodborne illness, is characterized by hemorrhagic colitis and, occasionally, hemolytic-uremic syndrome, especially in children and the elderly. Most cases arise from eating undercooked contaminated ground beef or other contaminated foods. The bacteria attach to the intestinal epithelium and inject a payload of pathogenetic molecules directly into the host cells. Shiga toxin (Stx) is one of the major virulence factors produced by EHEC, which has



been identified as a requirement for the development of hemorrhagic colitis and hemolytic-uremic syndrome. However, EHEC also causes an early, nonbloody form of diarrhea. Roxas *et al* reasoned that if they studied infection with Stx-negative EHEC they might identify novel aspects of early, Stx-independent pathogenesis.

Using mouse models, the authors found that Stx-negative EHEC preferentially colonized the cecum and colon and that infections were more substantial in streptomycin-treated mice. Importantly, their model showed several key features associated with pathogenesis—infected mice exhibited microvillous effacement, acute inflammation, and defects in epithelial barrier function. At the molecular level, EHEC infection was characterized by a redistribution of tight junction proteins. Roxas and colleagues' study demonstrates that Stx-negative EHEC is still capable of infection and colonic damage, albeit at a much less dramatic level than is expected from Stx-positive EHEC. This model should facilitate study of the early pathogenesis of EHEC, a point at which it might be more vulnerable to therapy.

Stellate cells are required for oval cell response in regenerating liver

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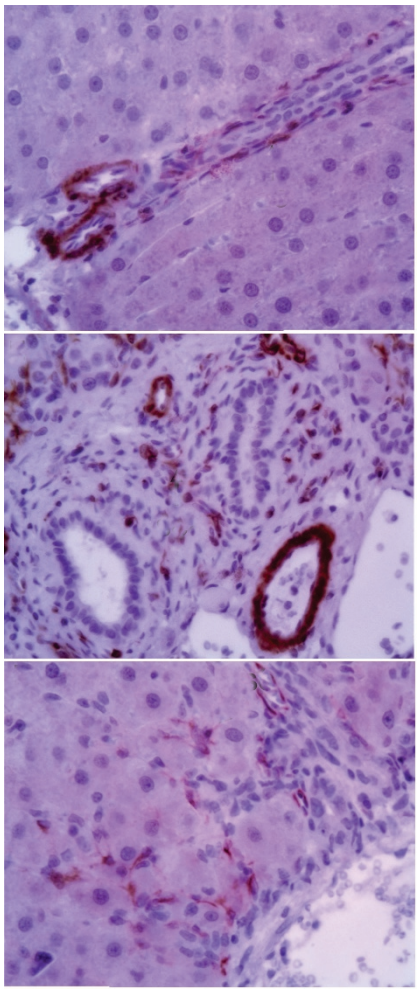
Liver regeneration is critical to hepatic homeostasis because the liver plays such a critical role in detoxifying the blood. The oval cell has been identified as the hepatic progenitor cell responsible for regenerating hepatocytes and biliary epithelium. Previous work has suggested an intimate relationship between hepatic stellate cells and oval cells. Recently, L-cysteine, a nonessential amino acid, has been shown to prevent stellate cell activation. To understand the relationship between stellate cells and oval cells during regeneration, Pintilie *et al* fed rats a diet rich in L-cysteine before initiation of a partial-hepatectomy protocol. They found that L-cysteine specifically inhibited proliferation of mesenchymal cells, including stellate cells, while having no effect on oval cells *in vitro*. Moreover, histological assessment after partial

hepatectomy showed a large decrease in stellate cell numbers in L-cysteine-fed rats. Decreases in stellate cells correlated with proportional decreases in oval cells.



Taking together these findings, the authors concluded that stellate cells are required for an appropriate oval cell response after partial hepatectomy. While many possible mechanisms have been proposed to explain how stellate cells stimulate oval cell proliferation and maintenance, including the production of various cytokines and an appropriate cell matrix, further studies are required to define the precise mechanism that determines the effect of stellate cells on the oval cell response during regeneration.

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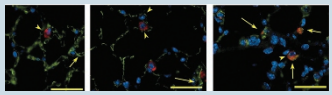
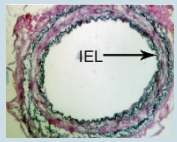
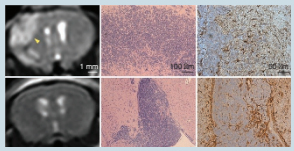


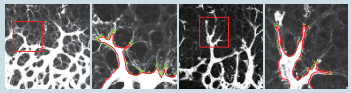
Mechanism of cigarette smoke–induced lung damage Emphysematous lung injury, a major component of chronic obstructive pulmonary disease, is due largely to cigarette smoking. Rtp801 (also known as Redd1, and encoded by *Ddit4*) is induced by hypoxia and DNA damage and is a negative regulator of mammalian target of rapamycin (mTOR). Because the mTOR signaling pathway has been implicated in emphysema, Tuder and colleagues asked whether Rtp801 might be involved in the pathogenesis of emphysema. They found that Rtp801 expression was activated by smoking-induced oxidative stress and that its expression inhibited mTOR signaling, resulting in both alveolar cell apoptosis and nuclear factor kappa β–induced inflammation. Thus, Rtp801 contributes to smoke-induced lung damage by at least two mechanisms, a finding that confirms its importance.
Nature Medicine, published online 16 May 2010; doi:10.1038/nm.2157



Prevention of transplant arteriosclerosis by regulatory T cells Transplant arteriosclerosis, a phenomenon of chronic rejection, is a serious problem associated with heart transplantation; the consequent ischemia limits the long-term utility of cardiac allografts. Immunologic pathways are thought to play a key role in the genesis of transplant arteriosclerosis. In a recent letter in *Nature Medicine*, Wood and colleagues describe their use of an ingenious chimeric humanized mouse model system to investigate the utility of regulatory T cells (Tregs) to inhibit transplant arteriosclerosis. They showed that treatment with Tregs that had been expanded *ex vivo* significantly inhibited transplant arteriosclerosis. Furthermore, they demonstrated that Tregs that expressed lower amounts of the interleukin-7 receptor ($CD127^{lo}$ Tregs) had a fivefold greater potency than $CD25^{hi}$ Tregs. These exciting data suggest that Treg cellular therapy has potential for the prevention of transplant arteriosclerosis.
Nature Medicine, published online 16 May 2010; doi:10.1038/nm.2154



An essential CREB3L2-ATF5-MCL1 survival pathway in malignant glioma Activating transcription factor-5 (ATF5) is a member of the ATF/cAMP responsive element–binding (CREB) family of transcription factors. ATF5 has antiapoptotic properties and is highly expressed in malignant gliomas. Loss of ATF5 induces apoptosis in malignant gliomas but not in normal neurons, which suggests that it would make a useful therapeutic target. As reported recently in *Nature Medicine*, Green and colleagues used a genome-wide RNA interference screen to delineate the upstream factors that control ATF5 expression. They discovered a previously unknown signal transduction pathway that leads to activation of the transcription factor CREB protein-3–like-2 (CREB3L2), which directly activates *ATF5* expression, resulting in transcriptional activation of myeloid cell leukemia sequence-1, an antiapoptotic protein. The pathway was validated as a therapeutic target via direct inhibition in mouse malignant glioma models, which demonstrated efficacy.
Nature Medicine 2010;16:671–677; doi:10.1038/nm.2158



Regulation of angiogenesis by ephrin-B2 Vascular remodeling is critical in normal and pathological processes. Ephrin-B2, a transmembrane ligand for Eph receptors, is necessary for early remodeling. Because ephrinB ligands are known to function as repulsive molecules for axon guidance, Sawamiphak *et al*, as described in a recent letter in *Nature*, hypothesized that ephrin-B2 might have a similar role in vessel guidance. Using mouse models with defective ephrin-B2 proteins, the authors found that ephrin-B2 reverse signaling regulates angiogenic sprouting and branching in both physiological and pathological angiogenesis. They also discovered that ephrin-B2 works by controlling vascular endothelial growth factor receptor (VEGFR)-2 internalization and signaling. In an accompanying letter, Wang *et al* report that ephrin-B2 has a similar function with respect to VEGFR-3. Thus, blocking ephrin-B2 might inhibit both VEGFR-2 and VEGFR-3, simultaneously inhibiting two important angiogenic signaling pathways.
Nature 2010; 465:487–491; doi:10.1038/nature08995
Nature 2010; 465:483–486; doi:10.1038/nature09002