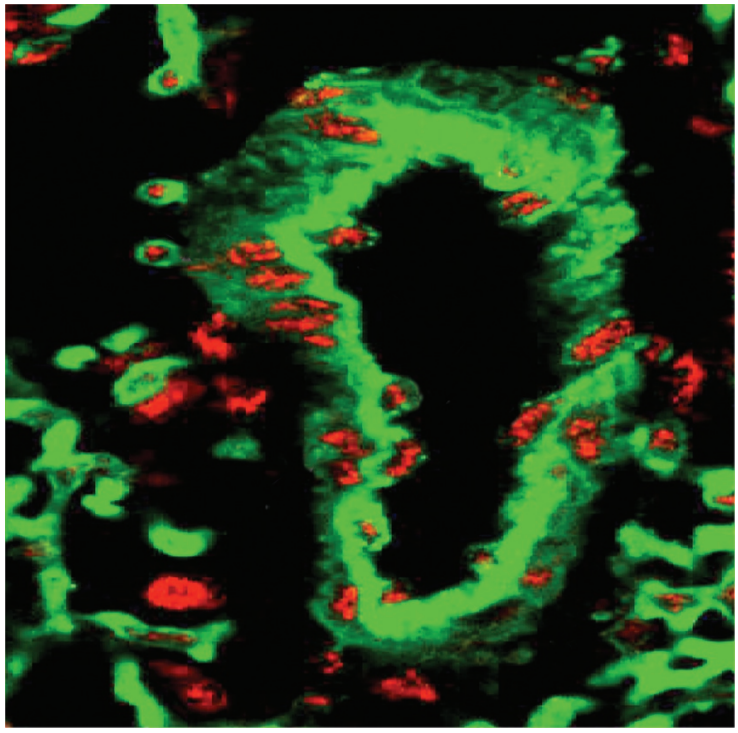
Laboratory Investigation (2009) 89, 2-3

INSIDE LI

doi:10.1038/labinvest.2008.119



Endoglin and activin receptor–like kinase 1: placing the suspects at the scene of the crime

See page 15

Pulmonary arteriovenous malformations (AVMs) can result in right-to-left shunts, leading to severe cyanosis and dyspnea. As its name implies, hereditary hemorrhagic telangiectasia (HHT) is an inherited disorder characterized by the development of telangiectasias (small dilated blood vessels) involving mucocutaneous surfaces. However, patients with HHT also develop AVMs involving brain, liver, and lungs. HHT is associated with mutations in endoglin (*ENG*) or activin receptor–like kinase 1 (*ACVRL*1, also known as *ALK1*), receptors within the transforming growth factor-β family. A second disorder, familial pulmonary artery hypertension (fPAH), is also associated with *ENG* or *ACVRL1* mutations, further implicating them in the pathogenesis of vascular disease.

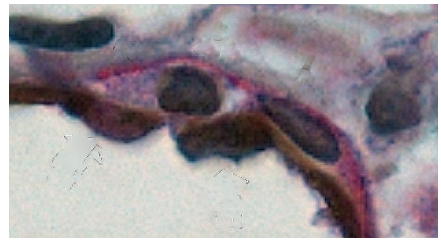
To understand how ENG and ACVRL1 contribute to fPAH and HHT, Mahmoud and coauthors performed a comprehensive survey of Eng and Acvrl1 expression in the developing murine lung in wild-type and *Eng* heterozygous knockout mice using protein and RNA-based expression techniques. They found that while Eng was more broadly expressed than Acvrl1, both Eng and Acvrl1 expression overlapped in distal arterioles, distal venules, and capillaries, the anatomic sites for telangiectasias. Therefore, they have placed both of these molecules at the site where the pathology occurs. This is an important step in understanding how these molecules contribute to the development of the vascular system and diseases that affect these sites. By localizing these proteins to different anatomic areas of the pulmonary vasculature, the elegant experiments described in this paper are sure to enhance our understanding of both developmental and disease processes involving the blood vessels of the lung.

Vascularization of human xenografts—not as simple as anticipated

See page 91

Human xenografts are a staple of cancer research. However, interpretation of xenograft studies is complicated by many issues related to mouse host–human cancer xenograft interactions. Sanz and colleagues have hit on an intriguing finding with widespread ramifications in human xenograft studies and cancer biology. They found that xenografts from human colorectal carcinoma specimens are colonized by mouse endothelial cells whereas blood vessels from renal cell carcinoma xenografts are lined by human endothelium.

Their study took advantage of species-specific anti-CD31 antibodies to differentiate between mouse and human endothelial cells. Interestingly, at early time points after engraftment of human colorectal carcinoma xenografts, mouse endothelial cells appear to use abandoned human basement membrane as a scaffold



for a host–tumor blood supply. Surprisingly, apoptosis does not appear to play a major role in the disappearance of human endothelial cells. At later time points after engraftment, the need for a human scaffold is lost and the new vasculature appears to develop entirely from murine components.

Differences in how human xenografts are vascularized after engraftment could be useful to generate a system to dissect many aspects of tumor vascularization. Furthermore, such a system has the potential to explain several mystifying

aspects of cancer biology, such as variations in the potential for metastasis to different anatomic sites. Ideally, as we further our understanding of human xenografts, they will be of greater use in understanding cancer biology and testing novel therapies.

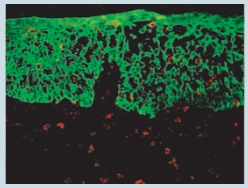
The interleukin-1 axis: a double-edged sword

See page 68

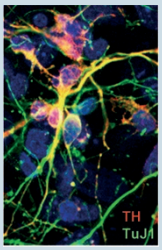
Acetaminophen (APAP) is one of the most common over-the-counter pain medications. Although this medication is generally safe, accidental or intentional overdose results in about 500 deaths due to liver toxicity each year in the United States. Liver toxicity is directly attributable to an APAP metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is generated by metabolism of APAP by the cytochrome P450 system. Previous work has shown that intrahepatic interleukin-1 (IL-1), a pleiotropic proinflammatory cytokine, is associated with APAP-induced liver injury. It was therefore a surprise to Ishibe and colleagues that loss of IL-1 receptor antagonist (IL-1 ra), effectively augmenting IL-1 signaling, attenuated the hepatotoxicity of APAP in a mouse IL-1 ra knockout model. They showed that the loss of hepatotoxicity was due to suppression of cytochrome P450 enzyme expression, resulting in a decrease in NAPQI formation. The mechanism of cytochrome P450 enzyme suppression was related to NF-κB activation resulting from loss of IL-1 ra. NF-κB activation directly suppresses intrahepatic expression of P450 enzymes.

Paradoxically, although increased IL-1 signaling blunts the early damage associated with APAP due to suppression of cytochrome P450 and decreased NAPQI, increased IL-1 at later times leads to increased hepatotoxicity as a result of indirect recruitment of pro-inflammatory leukocytes—a double-edged sword. This work suggests that, if these findings are to be exploited therapeutically, pro-IL-1 drugs need to be short-lived. Otherwise, the proinflammatory edge of the IL-1 sword could outweigh any benefit seen by IL-1-mediated decreases in NAPQI.

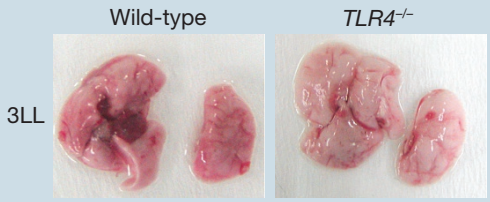
nature.com/pathology



New player in mucosal defense Two types of natural killer (NK) cells have been characterized: $CD56^{dim}$ plays a key role in lysis of cell targets in the blood, and $CD56^{bright}$ secretes interferon (IFN)-γ in lymph nodes. Recently, however, a novel type of NK cell, NKp44, was identified. A letter in *Nature* describes NKp44 and its important role in innate mucosal immunity. The cells, referred to as NK-22 cells, are preferentially located in mucosa-associated lymphoid tissues such as tonsils and Peyer's patches, where they secrete interleukin (IL)-22, IL-26, and leukemia inhibitory factor. They stimulate epithelial cells to secrete IL-10 and proliferate and express mitogenic and anti-apoptotic molecules. Furthermore, they appear in the small intestine of mice during bacterial infection and thus are poised to be important in the defense of mucosal sites.
Nature, published online 2 November 2008; doi:10.1038/nature07537



Pluripotent stem cells from hair? Induced pluripotent stem (iPS) cells can be derived by forced expression of a small number of genes in mouse and human cells. Although these cells have the potential to generate virtually any tissue for limitless applications, the process of deriving iPS cells is relatively inefficient. In a recent article in *Nature Biotechnology*, Aasen and colleagues showed that they could generate iPS cells via forced expression of *OCT4, SOX2, KLF4,* and *c-MYC* in human keratinocytes, which they termed KiPS (keratinocyte-derived iPS) cells. They found that the process is at least 100-fold more efficient and twice as fast as similar protocols used in reprogramming human fibroblasts. In a tour de force, they generated KiPS cells from single human hairs, making biopsy completely unnecessary. This work is certain to advance the field toward the eventual logical conclusion—the use of iPS cells in treating human disease.
Nature Biotechnology 2008;26:1276–1284; doi:10.1038/nbt.1503



New insights into how primary tumors talk to metastatic sites The seed-and-soil theory of metastasis was described more than 100 years ago, but only recently have we begun to understand the mechanisms behind this phenomenon. In a recent letter in *Nature Cell Biology*, Hiratsuka and colleagues shed further light on this interesting subject. Previous work from their lab has shown that primary tumor cells induced the expression of the chemotattractants S100A8 and S100A9 in the lung, which served to create a pro-inflammatory environment that is favorable for metastasis. In their current work, they reveal that S100A8 and S100A9 induce the expression of serum amyloid A 3 (SAA3), a chemotactic agonist for phagocytes. Expression of SAA3 induces the migration of Mac 1^{+}-myeloid cells to the lung. Furthermore, SAA3 induces its own secretion through a positive feedback loop mediated through Toll-like receptor 4 (TLR4) and NF-κB signaling. Inhibition of either TLR4 or SAA3 interfered with migration of primary tumor cells to the lung, indicating that inhibition of TLR4 and SAA3 may be a novel therapeutic strategy.
Nature Cell Biology 2008;10:1349–1355; doi:10.1038/ncb1794

New siRNA strategy delivers a double anti-tumor punch In a short time, short interfering RNAs (siRNAs) have become workhorses at the bench, and they are now beginning to make their way to the bedside. In a recent article in *Nature Medicine*, Poeck and colleagues describe a clever siRNA-based approach to treating cancer. Their strategy takes advantage of the traditional role of siRNAs in targeting *Bcl2* through RNA interference. In addition, they exploit the ability of the innate immune system to detect viral nucleic acids by the identification of RNA possessing a 5′-triphosphate by Rig-I helicase. They designed a straightforward anti-*Bcl2* siRNA containing a 5′-phosphate (3p-siRNA) and showed that inhibition of *Bcl2* expression and Rig-1-mediated cellular immunity synergized to induce extensive apoptosis in melanoma lung metastases *in vivo*. This innovative approach is certain to provoke further work using similar approaches.
Nature Medicine 2008;14:1256–1263; doi:10.1038/nm.1887